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(54) Title: SUBSTITUTED IMIDAZOQUINOLINES, IMIDAZONAPHTHYRIDINES, AND IMIDAZOPYRIDINES, COMPOSITIONS, AND METHODS

(57) Abstract: Certain 1*H*-imidazo[4,5-*c*]quinolines, 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolines, 1*H*-imidazo[4,5-*c*][1,5]naphthyridines, 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*][1,5]naphthyridines, and 1*H*-imidazo[4,5-*c*]pyridines substituted at the 1- and 2-positions, pharmaceutical compositions containing these compounds, methods of making the compounds, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases, are disclosed.

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# SUBSTITUTED IMIDAZOQUINOLINES, IMIDAZONAPHTHYRIDINES, AND IMIDAZOPYRIDINES, COMPOSITIONS, AND METHODS

## CROSS REFERENCE TO RELATED APPLICATIONS

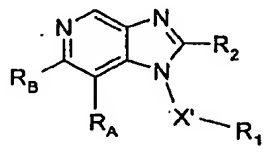
The present invention claims priority to U.S. Provisional Application Serial No. 60/751,392, filed December 16, 2005, which is incorporated herein by reference.

## BACKGROUND

Certain compounds have been found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders. However, there continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other means.

## SUMMARY OF THE INVENTION

It has now been found that certain substituted 1*H*-imidazo[4,5-*c*]quinolines, 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolines, 1*H*-imidazo[4,5-*c*][1,5]naphthyridines, 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*][1,5]naphthyridines, and 1*H*-imidazo[4,5-*c*]pyridines modulate cytokine biosynthesis. In one aspect, the present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula I, II, IIa, III, IV, IVa, V, or Va:



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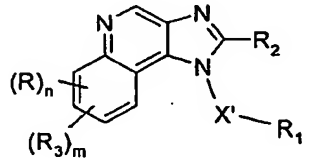

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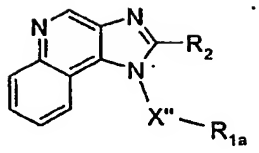
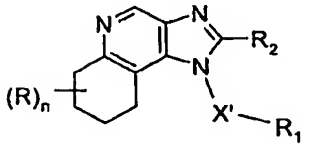


IIa



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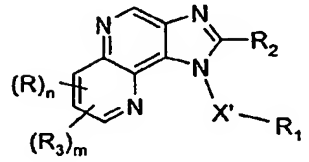
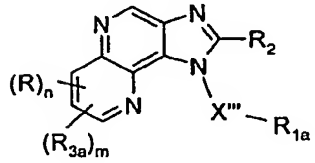
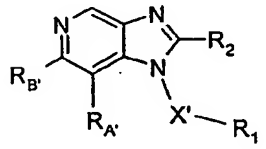


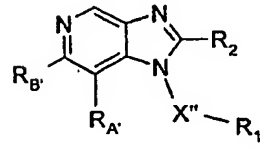
IV



IVa



V



Va

wherein R, $R_1$, $R_{1a}$, $R_2$, $R_3$, $R_{3a}$, $R_A$, $R_B$, $R_{A'}$, $R_{B'}$, X', X", X"', n, and m are as defined below; or pharmaceutically acceptable salts thereof.

The compositions comprising compounds or salts of Formulas I, II, IIa, III, IV, IVa, V, or Va are useful for modulating cytokine biosynthesis (e.g., inducing the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. The ability to modulate cytokine biosynthesis makes the compositions useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases that are responsive to such changes in the immune response.

In another aspect, the present invention also provides compounds of the Formulas IIa, III, IVa, and Va, and pharmaceutically acceptable salts thereof.

In another aspect, the present invention provides methods of inducing cytokine biosynthesis in animal cells, treating a viral disease in an animal, and/or treating a neoplastic disease in an animal by administering to the animal a compound or salt of Formulas IIa, III, IVa, and/or Va, or a pharmaceutical composition comprising one or more compounds of the Formulas I, II, IIa, III, IV, IVa, V, and/or Va, and/or pharmaceutically acceptable salts thereof.

In another aspect, the invention provides methods of synthesizing the compounds of Formulas I, II, IIa, III, IV, IVa, V, and Va and intermediate compounds useful in the synthesis of these compounds.

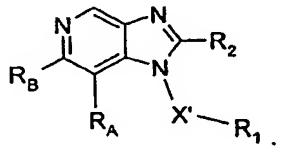
As used herein, "a", "an", "the", "at least one", and "one or more" are used interchangeably.

The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

## DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

In one aspect, the present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula I, II, IIa, III, IV, IVa, V, or Va:



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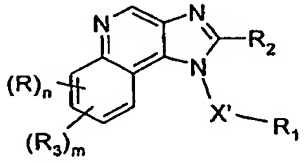

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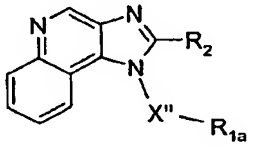
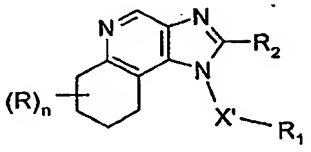
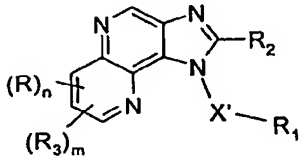


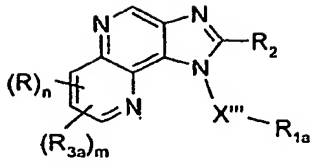
IIa



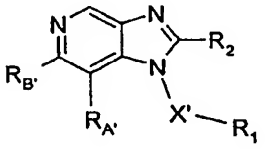
III



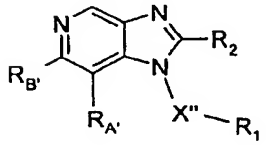
IV



IVa



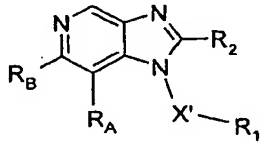
V



Va

wherein R, $R_1$, $R_{1a}$, $R_2$, $R_3$, $R_{3a}$, $R_A$, $R_B$, $R_{A'}$, $R_{B'}$, X', X'', X''', n, and m are as defined below; or pharmaceutically acceptable salts thereof.

In one embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula I:



I

wherein:

X' is selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$, -NH-, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of $-NH_2$, $-CH_3$, $-CH_2-C_{1-4}$ alkyl,

$-CH_2-C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, $-CH_2-O-C_{1-3}$ alkyl, $-CH_2-OH$, $-CH_2-C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

$R_A$ and $R_B$ taken together form a fused benzene or pyridine ring which is unsubstituted or substituted by one or two R groups, or substituted by one $R_3$ group, or substituted by one $R_3$ group and one R group; wherein the fused pyridine ring is

wherein the highlighted bond indicates the position where the ring is fused;

or $R_A$ and $R_B$ taken together form a fused cyclohexene or tetrahydropyridine ring which is unsubstituted or substituted at a carbon atom by one or more R groups; wherein the fused tetrahydropyridine ring is

wherein the highlighted bond indicates the position where the ring is fused;

or $R_A$ is alkyl, and $R_B$ is hydrogen or alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

$R_3$ is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$,

$-Z-X-R_5$, and

$-NH-Q-R_4$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and

alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

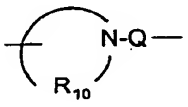
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

$-O-N=C(R_4)-$,

$-C(=N-O-R_8)-$,

$-CH(-N(-O-R_8)-Q-R_4)-$,



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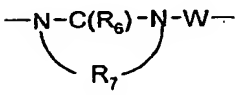

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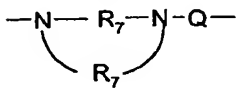

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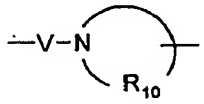

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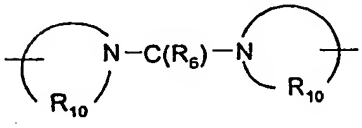
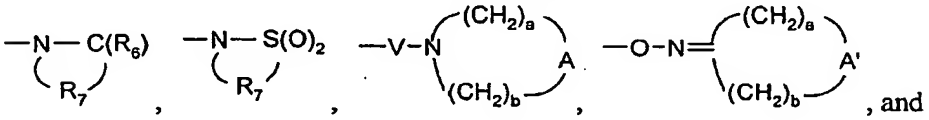


;

Z is a bond or -O-;

$R_4$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

$R_5$ is selected from the group consisting of:




;

$R_6$ is selected from the group consisting of =O and =S;

$R_7$ is $C_{2-7}$ alkylene;

$R_8$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, hydroxy-$C_{1-10}$ alkylenyl, $C_{1-10}$ alkoxy-$C_{1-10}$ alkylenyl, aryl-$C_{1-10}$ alkylenyl, and heteroaryl-$C_{1-10}$ alkylenyl;

$R_9$ is selected from the group consisting of hydrogen and alkyl;

$R_{10}$ is $C_{3-8}$ alkylene;

A is selected from the group consisting of -$CH_2$-, -O-, -C(O)-, -$S(O)_{0-2}$-, and –N(-Q-$R_4$)-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-$R_4$)-, and -$CH_2$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

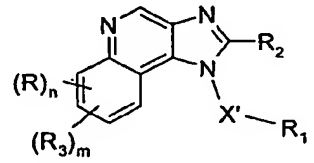
V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq 7$;

or a pharmaceutically acceptable salt thereof. In another embodiment of this pharmaceutical composition, X' is selected from the group consisting of $-CH_2-$, -NH-, and -O-; and $R_3$ is at the 7- or 8-position.

In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula II:



II

wherein:

X' is selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$, -NH-, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of $-NH_2$, $-CH_3$, $-CH_2-C_{1-4}$ alkyl, $-CH_2-C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, $-CH_2-O-C_{1-3}$ alkyl, $-CH_2-OH$, $-CH_2-C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

n is 0, 1, or 2;

$R_3$ is selected from the group consisting of:

-Z-$R_4$,

-Z-X-$R_4$,

-Z-X-Y-$R_4$,

-Z-X-Y-X-Y-$R_4$,

-Z-X-$R_5$, and

-NH-Q-$R_4$;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

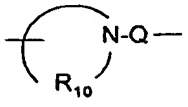
-$C(R_6)$-$N(OR_9)$-,

-O-$N(R_8)$-Q-,

-O-N=$C(R_4)$-;

-C(=N-O-$R_8$)-,

-CH(-N(-O-$R_8$)-Q-$R_4$)-,

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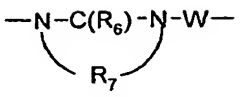
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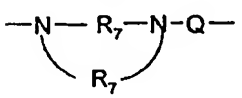
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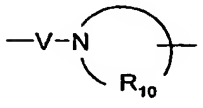
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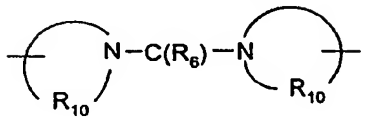
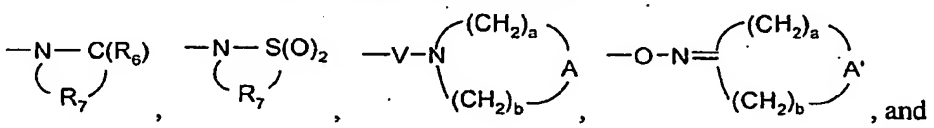

;

Z is a bond or -O-;

$R_4$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

$R_5$ is selected from the group consisting of: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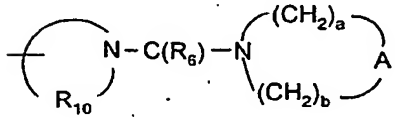

;

$R_6$ is selected from the group consisting of =O and =S;

$R_7$ is $C_{2-7}$ alkylene;

$R_8$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl,

hydroxy-$C_{1-10}$ alkylenyl, $C_{1-10}$ alkoxy-$C_{1-10}$ alkylenyl, aryl-$C_{1-10}$ alkylenyl, and heteroaryl-$C_{1-10}$ alkylenyl;

$R_9$ is selected from the group consisting of hydrogen and alkyl;

$R_{10}$ is $C_{3-8}$ alkylene;

A is selected from the group consisting of -$CH_2$-, -O-, -C(O)-, -$S(O)_{0-2}$-, and –N(-Q-$R_4$)-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-$R_4$)-, and -$CH_2$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

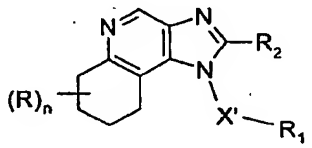
V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq 7$;

or a pharmaceutically acceptable salt thereof. In another embodiment of this pharmaceutical composition, X' is selected from the group consisting of -$CH_2$-, -NH-, and -O-; and $R_3$ is at the 7- or 8-position.

In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula III:




III

wherein:

X' is selected from the group consisting of -$CH_2$-, -$CH(CH_3)$-, -NH-, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of -$NH_2$, -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl,

-$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

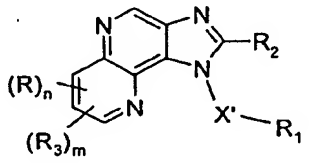
-$N(R_9)_2$;

n is 0, 1, or 2; and

$R_9$ is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof. In another embodiment of this pharmaceutical composition, X' is selected from the group consisting of -$CH_2$-, -NH-, and -O-.

In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula IV:



IV

wherein:

X' is selected from the group consisting of -$CH_2$-, -$CH(CH_3)$-, -NH-, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of -$NH_2$, -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl,

-$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

-$N(R_9)_2$;

n is 0, 1, or 2;

$R_3$ is selected from the group consisting of:

-Z-$R_4$,

-Z-X-$R_4$,

-Z-X-Y-$R_4$,

-Z-X-Y-X-Y-$R_4$,

-Z-X-$R_5$, and

-NH-Q-$R_4$;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

-O-C(O)-O-,

-N($R_8$)-Q-,

-C($R_6$)-N($R_8$)-,

-O-C($R_6$)-N($R_8$)-,

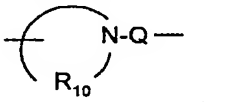
-C($R_6$)-N($OR_9$)-,

-O-N($R_8$)-Q-,

-O-N=C($R_4$)-,

-C(=N-O-$R_8$)-,

-CH(-N(-O-$R_8$)-Q-$R_4$)-,



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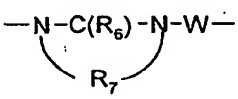

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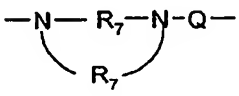

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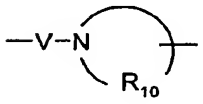

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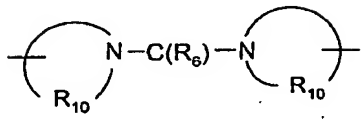


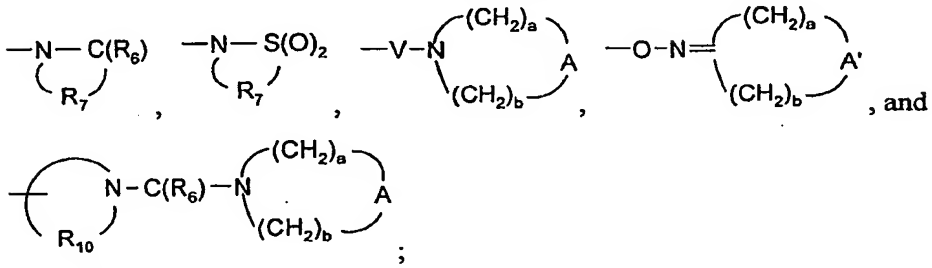
;

Z is a bond or -O-;

$R_4$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino;

(dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

$R_5$ is selected from the group consisting of:



;

$R_6$ is selected from the group consisting of =O and =S;

$R_7$ is $C_{2-7}$ alkylene;

$R_8$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, hydroxy-$C_{1-10}$ alkylenyl, $C_{1-10}$ alkoxy-$C_{1-10}$ alkylenyl, aryl-$C_{1-10}$ alkylenyl, and heteroaryl-$C_{1-10}$ alkylenyl;

$R_9$ is selected from the group consisting of hydrogen and alkyl;

$R_{10}$ is $C_{3-8}$ alkylene;

A is selected from the group consisting of -$CH_2$-, -O-, -C(O)-, -$S(O)_{0-2}$-, and –N(-Q-$R_4$)-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-$R_4$)-, and -$CH_2$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

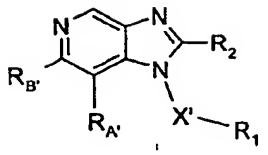
V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq 7$;

or a pharmaceutically acceptable salt thereof. In another embodiment of this pharmaceutical composition, X' is selected from the group consisting of -$CH_2$-, -NH-, and -O-; and $R_3$ is at the 7- or 8-position.

In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula V:



V

wherein:

X' is selected from the group consisting of -$CH_2$-, -$CH(CH_3)$-, -NH-, and -O-;

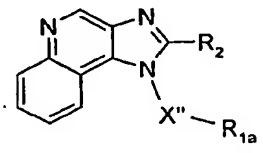
$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of -$NH_2$, -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl, -$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

$R_{A'}$ is alkyl, and $R_{B'}$ is hydrogen or alkyl;

or a pharmaceutically acceptable salt thereof. In another embodiment of this pharmaceutical composition, X' is selected from the group consisting of -$CH_2$-, -NH-, and -O-.

In another embodiment, the present invention provides a compound of Formula IIa:



IIa

wherein:

X" is selected from the group consisting of -$CH_2$-, -$CH(CH_3)$-, and -O-;

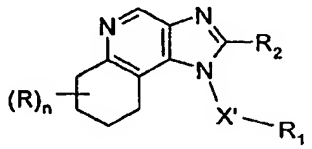
$R_{1a}$ is selected from the group consisting of tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl; and

$R_2$ is selected from the group consisting of -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl,

-$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

or a pharmaceutically acceptable salt thereof. In another embodiment of the compound of Formula IIa or a pharmaceutically acceptable salt thereof, X" is -$CH_2$-.

In another embodiment, the present invention provides a compound of Formula III:



III

wherein:

X' is selected from the group consisting of -$CH_2$-, -$CH(CH_3)$-, -NH-, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl; tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of -$NH_2$, -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl, -$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

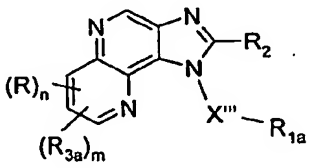
-$N(R_9)_2$;

n is 0, 1, or 2; and

$R_9$ is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof. In another embodiment of the compound of Formula III or a pharmaceutically acceptable salt thereof, X' is selected from the group consisting of -$CH_2$-, -NH-, and -O-.

In another embodiment, the present invention provides a compound of Formula IVa:



IVa

wherein:

X''' is selected from the group consisting of -$CH_2$- and -$CH(CH_3)$-;

$R_{1a}$ is selected from the group consisting of tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of -$NH_2$, -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl, -$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

-$N(R_9)_2$;

n is 0 or 1;

$R_{3a}$ is selected from the group consisting of:

-Z-$R_4$, and

-Z-X-$R_4$;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

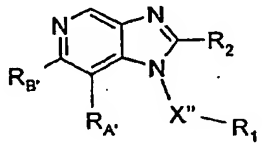
Z is a bond or -O-;

$R_4$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and

$R_9$ is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof. In another embodiment of the compund of Formula IVa or a pharmaceutically acceptable salt thereof, X''' is $-CH_2-$; and $R_3$ is at the 7- or 8-position.

In another embodiment, the present invention provides a compound of Formula Va:



Va

wherein:

X'' is selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of $-NH_2$, $-CH_3$, $-CH_2-C_{1-4}$ alkyl, $-CH_2-C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, $-CH_2-O-C_{1-3}$ alkyl, $-CH_2-OH$, $-CH_2-C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

$R_{A'}$ is alkyl, and $R_{B'}$ is hydrogen or alkyl;

or a pharmaceutically acceptable salt thereof. In another embodiment of the compound of Formula Va or a pharmaceutically acceptable salt thereof, X" is $-CH_2-$.

For any of the compounds presented herein, each one of the following variables (e.g., R, $R_1$, $R_{1a}$, $R_2$, $R_3$, $R_{3a}$, $R_A$, $R_B$, $R_{A'}$, $R_{B'}$, $R_4$, X, X', X", X'", Y, Z, A, Q, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables describes a compound or compounds which is an embodiment of the present invention, or which in combination with a pharmaceutically acceptable carrier is a composition which is an embodiment of the present invention.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, $R_A$ and $R_B$ taken together form a fused benzene or pyridine ring which is unsubstituted or substituted by one or two R groups, or substituted by one $R_3$ group, or substituted by one $R_3$ group and one R group; wherein the fused pyridine ring is

wherein the highlighted bond indicates the position where the ring is fused;

or $R_A$ and $R_B$ taken together form a fused cyclohexene or tetrahydropyridine ring which is unsubstituted or substituted at a carbon atom by one or more R groups; wherein the fused tetrahydropyridine ring is

wherein the highlighted bond indicates the position where the ring is fused;

or $R_A$ is alkyl, and $R_B$ is hydrogen or alkyl.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, $R_A$ and $R_B$ taken

together form a fused benzene or pyridine ring which is unsubstituted or substituted by one or two R groups, or substituted by one $R_3$ group, or substituted by one $R_3$ group and one R group; wherein the fused pyridine ring is

wherein the highlighted bond indicates the position where the ring is fused. For certain of these embodiments, $R_A$ and $R_B$ taken together form the fused benzene ring which is unsubstituted or substituted by one or two R groups, or substituted by one $R_3$ group, or substituted by one $R_3$ group and one R group. For certain of these embodiments, the fused benzene ring is unsubstituted. Alternatively, for certain of these embodiments, $R_A$ and $R_B$ taken together form the fused pyridine ring which is unsubstituted or substituted by one or two R groups, or substituted by one $R_3$ group, or substituted by one $R_3$ group and one R group. For certain of these embodiments, the fused pyridine ring is unsubstituted.

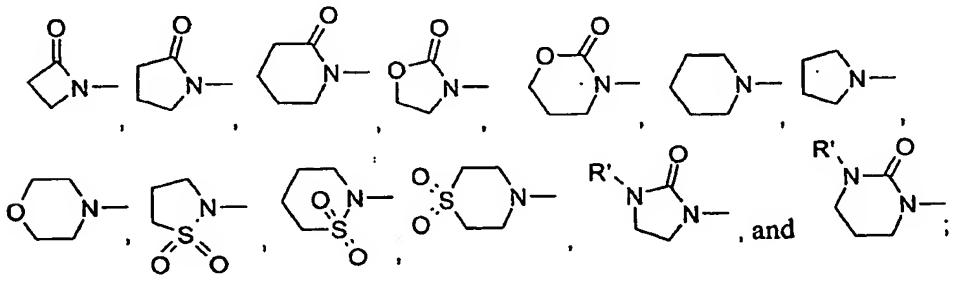
For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, $R_A$ and $R_B$ taken together form a fused cyclohexene or tetrahydropyridine ring which is unsubstituted or substituted at a carbon atom by one or more R groups; wherein the fused tetrahydropyridine ring is

wherein the highlighted bond indicates the position where the ring is fused. For certain of these embodiments, $R_A$ and $R_B$ taken together form a fused cyclohexene ring which is unsubstituted or substituted by one or more R groups. For certain of these embodiments, the fused cyclohexene ring is unsubstituted. Alternatively, for certain of these embodiments, $R_A$ and $R_B$ taken together form the fused tetrahydropyridine ring which is unsubstituted or substituted at a carbon atom by one or more R groups. For certain of these embodiments, the fused tetrahydropyridine ring is unsubstituted.

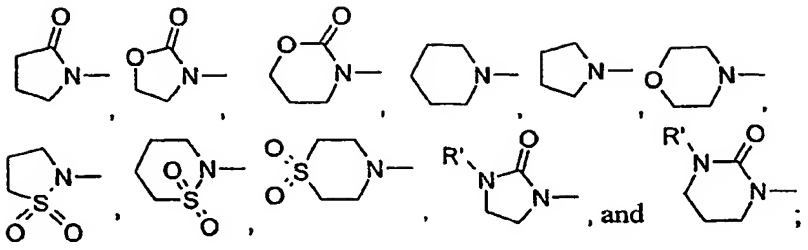
For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, $R_A$ is alkyl, and $R_B$ is hydrogen or alkyl. For certain of these embodiments, $R_A$ and $R_B$ are both methyl.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula V, or a pharmaceutically acceptable salt thereof, $R_{A'}$ is alkyl, and $R_{B'}$ is hydrogen or alkyl. For certain of these embodiments, $R_{A'}$ and $R_{B'}$ are both methyl.

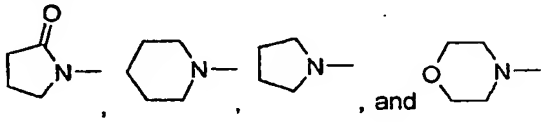
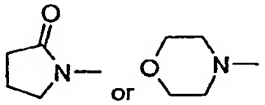
For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I, II, or IV, or a pharmaceutically acceptable salt thereof, or of any one of the above embodiments which includes $R_3$, $R_3$ is selected from the group consisting of -Z-$R_4$, -Z-X-$R_4$, -Z-X-Y-$R_4$, -Z-X-Y-X-Y-$R_4$, -Z-X-$R_5$, and -NH-Q-$R_4$. For certain of these embodiments, $R_3$ is -Z-$R_4$. For certain of these embodiments, $R_4$ is selected from the group consisting of aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl wherein the aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, aminoalkyl, halogen, hydroxy, cyano, amino, alkylamino, and dialkylamino; and Z is a bond. For certain of these embodiments, $R_3$ is selected from the group consisting of hydroxyphenyl, (hydroxymethyl)phenyl, (aminomethyl)phenyl, pyridin-3-yl, and pyridin-4-yl. Alternatively, for certain of these embodiments where $R_3$ is -Z-$R_4$, $R_4$ is a heterocyclyl group which contains one or more nitrogen atoms and optionally a ring oxygen or ring sulfur atom, wherein the point of attachment of the heterocyclyl group is one of the nitrogen atoms, and wherein the heterocyclyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of oxo, alkyl, aryl, and arylalkylenyl; and Z is a bond. For certain of these embodiments, the heterocyclyl group is monocyclic and contains 4 to 6 ring atoms. For certain of these embodiments, the heterocyclyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of oxo, alkyl, and arylalkylenyl. For certain of these embodiments, the heterocyclyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of oxo and alkyl. For certain of these embodiments, the heterocyclyl group is selected from the group consisting of:

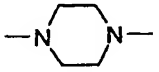


wherein R' is alkyl. For certain of these embodiments, the heterocyclyl group is selected from the group consisting of:


; wherein R' is alkyl.

For certain of these embodiments, the heterocyclyl group is selected from the group consisting of:


. For certain of these embodiments, the heterocyclyl group is 
.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I, II, or IV, or a pharmaceutically acceptable salt thereof, or of any one of the above embodiments which includes $R_3$, $R_3$ is -Z-X-Y-$R_4$, except where $R_3$ is -Z-$R_4$. For certain of these embodiments, $R_4$ is selected from the group consisting of hydrogen, alkyl, and heterocyclyl; Y is selected from the group consisting of -$S(O)_2$-, -C(O)-, -C(O)-NH-, and -NH-$S(O)_2$-; X is phenylene; and Z is a bond. For certain of these embodiments, $R_3$ is (methylsulfonylamino)phenyl (e.g., $R_4$ is methyl and Y is -NH-$S(O)_2$-). Alternatively, for certain of these embodiments, $R_4$ is selected from the group consisting of alkyl, aryl, arylalkylenyl, and heteroaryl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, and alkyl; Y is selected from the group consisting of -$S(O)_2$-, -C(O)-, and -C(O)-N($R_8$)-; X is 
; and Z is a bond. Alternatively, for certain of these embodiments where $R_3$ is -Z-X-Y-$R_4$, $R_4$ is hydrogen or alkyl; Y is -C(O)-N($R_8$)- or -C(O)-O-; $R_8$ is $C_{1-4}$ alkyl; X is alkylene or alkenylene; and Z is a bond. For certain of these embodiments, $R_4$ is $C_{1-4}$ alkyl; Y is -C(O)-N($R_8$)-; and X is alkylene. Alternatively, for certain of these embodiments where $R_3$ is -Z-X-Y-$R_4$, $R_4$ is alkyl

substituted by maleimidyl; Y is -NHC(O)-; X is alkylene interrupted by one -O- group; and Z is -O-.

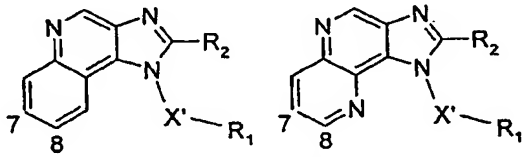
For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, $R_3$ is selected from the group consisting of hydroxyphenyl, (hydroxymethyl)phenyl, 4-(aminomethyl)phenyl, 3-(methylsulfonylamino)phenyl, pyridin-3-yl, and pyridin-4-yl.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I or IV, or a pharmaceutically acceptable salt thereof, $R_3$ is selected from the group consisting of hydroxyphenyl, (hydroxymethyl)phenyl, and (methylsulfonylamino)phenyl.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I, II, or IV, or a pharmaceutically acceptable salt thereof, or of any one of the above embodiments which includes $R_3$, $R_3$ is -Z-X-Y-X-Y-$R_4$ except where $R_3$ is -Z-$R_4$ or -Z-X-Y-$R_4$. For certain of these embodiments, $R_3$ is -Z-$X_f$-$Y_a$-$X_g$-$Y_b$-$R_4$ wherein $R_4$ is hydrogen or $C_{1-4}$ alkyl, $Y_b$ is -C(O)-O-, $X_g$ is alkylene, $Y_a$ is -NHC(O)-, $X_f$ is alkylene interrupted by one -O- group, and Z is -O-.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I, II, or IV, or a pharmaceutically acceptable salt thereof, or of any one of the above embodiments which includes $R_3$, $R_3$ is -NH-Q-$R_4$ except where $R_3$ is -Z-$R_4$, -Z-X-Y-$R_4$, or -Z-X-Y-X-Y-$R_4$. For certain of these embodiments, Q is -C(O)-, -C(O)-O-, -C(O)-N($R_8$)-, or -$S(O)_2$-, and $R_4$ is alkyl, aryl, arylalkylenyl or heteroaryl, each of which is unsubstituted or substituted by one or more substituents independently selected from halogen, hydroxy, and alkyl. For certain of these embodiments, $R_8$ is hydrogen or $C_{1-4}$ alkyl. For certain of these embodiments, Q is -C(O)-, and $R_4$ is alkyl or aryl. For certain of these embodiments, Q is -$S(O)_2$-, and $R_4$ is alkyl or aryl. Alternatively, for certain of these embodiments, Q is -C(O)- and $R_4$ is heterocyclyl which is unsubstituted or substituted by one or more substituents independently selected form the group consisting of alkyl and oxo; and wherein heterocyclyl is a heterocyclyl group which contains one or more nitrogen atoms, wherein the point of attachment of the heterocyclyl group is one of the nitrogen atoms. For certain of these embodiments, the heterocyclyl group is monocyclic and contains 5 or 6 ring atoms. For certain of these embodiments, $R_4$ is piperidin-1-yl.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I, II, or IV, or a pharmaceutically acceptable salt thereof, or of any one of the above embodiments which includes $R_3$ (or $R_{3a}$), $R_3$ (or $R_{3a}$) is at the 7- or 8-position. For certain of these embodiments, $R_3$ (or $R_{3a}$) is at the 7-position. Alternatively, for certain of these embodiments, $R_3$ (or $R_{3a}$) is at the 8-position. The locations of the 7- and 8-positions are shown in the following formulas:



For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula II, III, or IV, or a pharmaceutically acceptable salt thereof, or of any one of the above embodiments which includes n, n is 0.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula II, III, or IV, or a pharmaceutically acceptable salt thereof, R is selected from the group consisting of halogen, hydroxy, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$. For certain of these embodiments, R is hydroxy or $-N(R_9)_2$. For certain of these embodiments, R is $-N(R_9)_2$. For certain of these embodiments, $R_9$ is hydrogen. Alternatively, for certain of these embodiments, $R_9$ is alkyl. For certain of these embodiments, m is 0 and n is 1. For certain of these embodiments, R is at the 7-position. For certain of these embodiments, R is at the 8-position.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula II or IV, or a pharmaceutically acceptable salt thereof, m is 0.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula II or IV, or a pharmaceutically acceptable salt thereof, m and n are both 0.

For certain embodiments, including any one of the above embodiments, $R_2$ is selected from the group consisting of $-NH_2$, $-CH_3$, $-CH_2-C_{1-4}$ alkyl, $-CH_2-C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, $-CH_2-O-C_{1-3}$ alkyl, $-CH_2-OH$, $-CH_2-C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen,

$C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl. For certain of these embodiments, $R_2$ is selected from the group consisting of $-CH_3$, $-CH_2-C_{1-4}$ alkyl, $-CH_2-O-C_{1-3}$ alkyl, $-CH_2-C_{1-2}$ alkylenyl-$O-C_{1-2}$ alkyl, $-CH_2-OH$, and $-CH_2-C_{1-3}$ alkylenyl-OH. For certain of these embodiments, $R_2$ is selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, cyclopropylmethyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl. For certain of these embodiments, $R_2$ is selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, cyclopropylmethyl, methoxymethyl, ethoxymethyl, and 2-methoxyethyl. For certain of these embodiments, $R_2$ is selected from the group consisting of *n*-propyl, *n*-butyl, methoxymethyl, ethoxymethyl, and 2-methoxyethyl.

For certain embodiments, including any one of the above embodiments, $R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl. For certain of these embodiments, $R_1$ is tetrahydo-2*H*-pyran-4-yl.

For certain embodiments, including any one of the above embodiments where X' is present, X' is selected from the group consisting of $-CH_2-$, -NH-, and -O-. Alternatively, for certain of these embodiments, X' is $-CH_2-$. Alternatively, for certain of these embodiments, X' is -NH-. Alternatively, for certain of these embodiments, X' is -O-.

For certain embodiments, e.g., of Formula Va, $R_{A'}$ is alkyl, and $R_{B'}$ is hydrogen or alkyl. For certain of these embodiments, $R_{A'}$ and $R_{B'}$ are both methyl.

For certain embodiments, e.g., of Formula IIa or any of the above embodiments of Formula Va, X" is selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$, and -O- except where X" is $-CH_2-$. For certain of these embodiments, X" is $-CH_2-$.

For certain embodiments, e.g., of Formula IVa, X'" is $-CH_2-$.

For certain embodiments, including any one of the above embodiments of Formula IVa, m is 1, and $R_{3a}$ is selected from the group consisting of $-Z-R_4$ and $-Z-X-R_4$. For certain of these embodiments, $R_{3a}$ is selected from the group consisting of hydroxyphenyl and (hydroxymethyl)phenyl.

For certain embodiments, including any one of the above embodiments of Formula III or IVa, R is selected from the group consisting of halogen, hydroxy, alkyl, haloalkyl,

alkoxy, and -N($R_9$)$_2$. For certain of these embodiments, R is hydroxy. For certain of these embodiments n is 1.

For certain embodiments, including any one of the above embodiments of Formula III or IVa, n is 0 except where n is 1.

For certain embodiments, including any one of the above embodiments of Formula IVa, m is 0 except where m is 1.

For certain embodiments, including any one of the above embodiments of Formula IVa, m and n are both 0 except where m or n is 1.

For certain embodiments, including any one of the above embodiments of Formula IIa or IVa, $R_{1a}$ is selected from the group consisting of tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl. For certain of these embodiments, $R_{1a}$ is tetrahydo-2*H*-pyran-4-yl.

For certain embodiments, including any one of the above embodiments of Formula III or Va, $R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl. For certain of these embodiments, $R_1$ is tetrahydo-2*H*-pyran-4-yl.

For certain embodiments, including any one of the above embodiments, of Formula IIa, III, IVa, or Va, $R_2$ is selected from the group consisting of -$NH_2$, -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl, -$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl. For certain of these embodiments, $R_2$ is selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, cyclopropylmethyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl. For certain of these embodiments, $R_2$ is selected from the group consisting of *n*-propyl, *n*-butyl, methoxymethyl, ethoxymethyl, and 2-methoxyethyl.

For certain embodiments, $R_4$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl

wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.

For certain embodiments, $R_4$ is selected from the group consisting of alkyl, aryl, heteroaryl, and arylalkylenyl wherein the aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, aminoalkyl, halogen, hydroxy, cyano, amino, alkylamino, and dialkylamino.

For certain embodiments, $R_4$ is selected from the group consisting of aryl and heteroaryl each of which is unsubstituted or substituted by hydroxy, hydroxyalkyl, or aminoalkyl.

For certain embodiments, $R_4$ is selected from the group consisting of hydroxyphenyl, (hydroxymethyl)phenyl, (aminomethyl)phenyl, pyridin-3-yl, and pyridin-4-yl.

For certain embodiments, $R_4$ is alkyl, aryl, arylalkylenyl or heteroaryl, each of which is unsubstituted or substituted by one or more substituents independently selected from halogen, hydroxy, and alkyl.

For certain embodiments, $R_4$ is alkyl or aryl.

For certain embodiments, $R_4$ is selected from the group consisting of hydrogen, alkyl, and heterocyclyl.

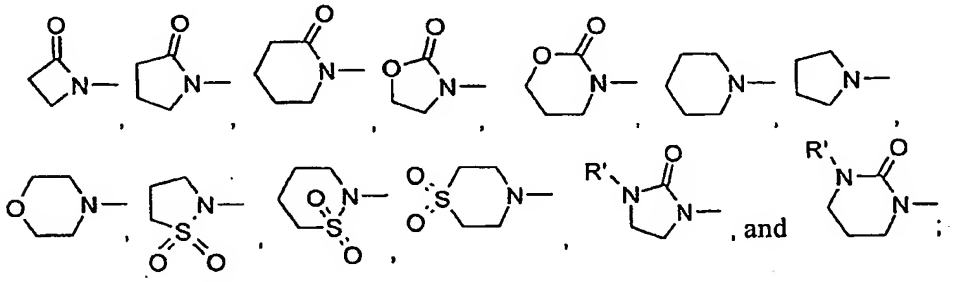
For certain embodiments, $R_4$ is hydrogen.

For certain embodiments, $R_4$ is alkyl.

For certain embodiments, $R_4$ is a heterocyclyl group which contains one or more ring nitrogen atoms and optionally a ring oxygen or ring sulfur atom, wherein the point of attachment of the heterocyclyl group is one of the nitrogen atoms, and wherein the heterocyclyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of oxo, alkyl, aryl, and arylalkylenyl.

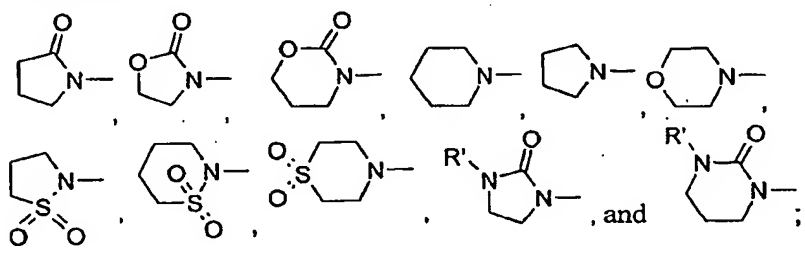
For certain embodiments the heterocyclyl group is monocyclic and contains 4 to 6 ring atoms. For certain of these embodiments, the heterocyclyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of oxo, alkyl, and arylalkylenyl. For certain of these embodiments, the heterocyclyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of oxo and alkyl.

For certain embodiments, $R_4$ is a heterocyclyl group selected from the group consisting of:



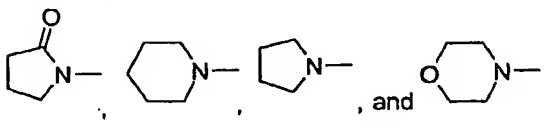
wherein R' is alkyl.

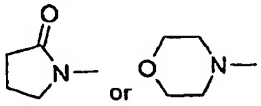
For certain embodiments, $R_4$ is a heterocyclyl group selected from the group consisting of:



wherein R' is alkyl,

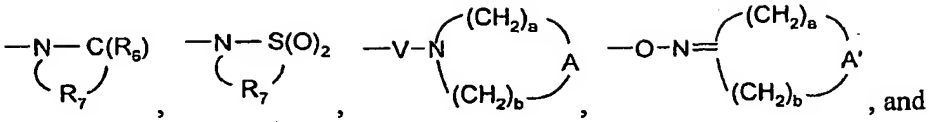
For certain embodiments, $R_4$ is a heterocyclyl group selected from the group consisting of:

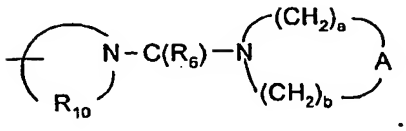


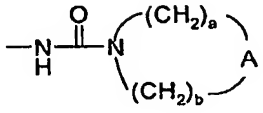
For certain embodiments, $R_4$ is 

For certain embodiments, $R_4$ is piperidin-1-yl.

For certain embodiments, $R_5$ is selected from the group consisting of:


, and





For certain embodiments, $R_5$ is

For certain embodiments, $R_6$ is selected from the group consisting of =O and =S.

For certain embodiments, $R_6$ is =O.

For certain embodiments, $R_6$ is =S.

For certain embodiments, $R_7$ is $C_{2-7}$ alkylene.

For certain embodiments, $R_7$ is $C_{2-4}$ alkylene.

For certain embodiments, $R_8$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, hydroxy-$C_{1-10}$ alkylenyl, $C_{1-10}$ alkoxy-$C_{1-10}$ alkylenyl, aryl-$C_{1-10}$ alkylenyl, and heteroaryl-$C_{1-10}$ alkylenyl.

For certain embodiments, $R_8$ is hydrogen, $C_{1-10}$ alkyl, or hydroxy-$C_{1-10}$ alkylenyl.

For certain embodiments, $R_8$ is $C_{1-4}$ alkyl.

For certain embodiments, $R_8$ is hydrogen.

For certain embodiments, $R_9$ is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, $R_9$ is hydrogen.

For certain embodiments, $R_9$ is alkyl.

For certain embodiments, $R_{10}$ is $C_{3-8}$ alkylene.

For certain embodiments, $R_{10}$ is pentylene.

For certain embodiments, R' is hydrogen, alkyl, or aryl.

For certain embodiments, R' is alkyl.

For certain embodiments, R' is hydrogen.

For certain embodiments, A is selected from the group consisting of -$CH_2$-, -O-, -C(O)-, -$S(O)_{0-2}$-, and –N(-Q-$R_4$)-.

For certain embodiments, A is selected from the group consisting of -$CH_2$-, -O-, and –N(alkyl)-.

For certain embodiments, A is -O-.

For certain embodiments, A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -$N(-Q-R_4)$-, and -$CH_2$-.

For certain embodiments, Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-.

For certain embodiments, Q is selected from the group consisting of -C(O)-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-, -$S(O)_2$-$N(R_8)$-, -C(O)-O-, and -C(O)-S-.

For certain embodiments, Q is -C(O)-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-, or -$S(O)_2$-$N(R_8)$-.

For certain embodiments, Q is -$C(R_6)$-.

For certain embodiments, Q is a bond.

For certain embodiments, V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-.

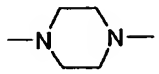
For certain embodiments, V is -$N(R_8)$-C(O)-.

For certain embodiments, W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-.

For certain embodiments, W is a bond.

For certain embodiments, X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups.

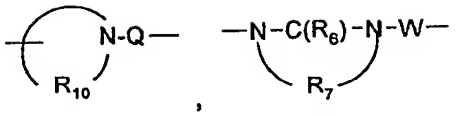
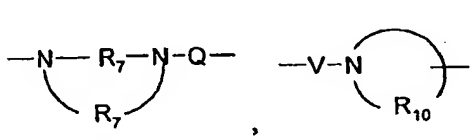
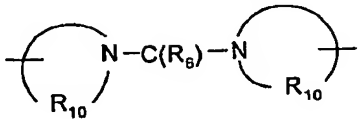
For certain embodiments, X is phenylene.

For certain embodiments, X is  .

For certain embodiments, X is $C_{1-4}$ alkylene.

For certain embodiments, X is methylene.

For certain embodiments, Y is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-, -$C(R_6)$-O-, -O-$C(R_6)$-, -O-C(O)-O-, -$N(R_8)$-Q-, -$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, -$C(R_6)$-$N(OR_9)$-, -O-$N(R_8)$-Q-, -O-N=$C(R_4)$-,

-C(=N-O-$R_8$)-, -CH(-N(-O-$R_8$)-Q-$R_4$)-,  , ,  , , and  .

For certain embodiments, Y is -N($R_8$)-Q-.

For certain embodiments, Y is selected from the group consisting of –N($R_8$)-C(O)-, -N($R_8$)-S(O)$_2$-, –N($R_8$)-C($R_6$)-N($R_8$)-, –N($R_8$)-S(O)$_2$-N($R_8$)-, -N($R_8$)-C($R_6$)-O-, and -N($R_8$)-C($R_6$)-S-.

For certain embodiments, Y is selected from the group consisting of -S(O)$_2$-, - C(O)-, -C(O)-NH-, and -NH-S(O)$_2$-.

For certain embodiments, Y is selected from the group consisting of -S(O)$_2$-, -C(O)-, and -N($R_8$)-C(O)-.

For certain embodiments, Z is a bond or -O-.

For certain embodiments, Z is a bond.

For certain embodiments, Z is -O-.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq 7$. For certain embodiments, a and b are each independently 1, 2, or 3. For certain embodiments, a and b are each 2.

For certain embodiments, m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1.

For certain embodiments, m is 1, and n is 0 or 1.

For certain embodiments, m is 1, and n is 0.

For certain embodiments, m is 0.

For certain embodiments, n is 0, 1, or 2.

For certain embodiments, n is 1.

For certain embodiments, n is 0.

For certain embodiments, m is 0, and n is 0.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I, II, III, IV, IVa, V, or Va, or a pharmaceutically acceptable salt

thereof, or of a compound or salt of Formula III, IVa, or Va, or of any one of the above embodiments which includes an $-NH_2$ group in a Formula, for example when $R_2$ is $-NH_2$, the $-NH_2$ group can be replaced by an -NH-$G_1$ group, to form prodrugs. In such embodiments, $G_1$ is selected from the group consisting of: -C(O)-R", α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R", -C(O)-N(R"')R", -C(=$NY_2$)-R", -CH(OH)-C(O)-$OY_2$, -CH($OC_{1-4}$ alkyl)$Y_0$, -$CH_2Y_1$, and -$CH(CH_3)Y_1$. For certain embodiments, $G_1$ is selected from the group consisting of -C(O)-R", α-aminoacyl, α-aminoacyl-α-aminoacyl, and -C(O)-O-R". Preferably, R" and R"' are independently selected from the group consisting of $C_{1-10}$ alkyl, $C_{3-7}$ cycloalkyl, phenyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, $C_{1-6}$ alkyl, $C_{1-4}$ alkoxy, aryl, heteroaryl, aryl$C_{1-4}$ alkylenyl, heteroaryl$C_{1-4}$ alkylenyl, halo$C_{1-4}$ alkylenyl, halo$C_{1-4}$ alkoxy, -O-C(O)-$CH_3$, -C(O)-O-$CH_3$, -C(O)-$NH_2$, -O-$CH_2$-C(O)-$NH_2$, -$NH_2$, and $-S(O)_2-NH_2$, with the proviso that R"' can also be hydrogen. Preferably, α-aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids. Preferably, $Y_2$ is selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, and benzyl. Preferably, $Y_0$ is selected from the group consisting of $C_{1-6}$ alkyl, carboxy$C_{1-6}$ alkylenyl, amino$C_{1-4}$ alkylenyl, mono-*N*-$C_{1-6}$ alkylamino$C_{1-4}$ alkylenyl, and di-*N,N*-$C_{1-6}$ alkylamino$C_{1-4}$ alkylenyl. Preferably, $Y_1$ is selected from the group consisting of mono-*N*-$C_{1-6}$ alkylamino, di-*N,N*-$C_{1-6}$ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-$C_{1-4}$ alkylpiperazin-1-yl.

For certain embodiments, including any one of the above embodiments where $G_1$ is present, $G_1$ is selected from the group consisting of -C(O)-R', α-aminoacyl, and -C(O)-O-R'.

For certain embodiments, including any one of the above embodiments where $G_1$ is present, $G_1$ is selected from the group consisting of -C(O)-R', α-amino-$C_{2-11}$ acyl, and -C(O)-O-R'. α-Amino-$C_{2-11}$ acyl includes α-amino acids containing a total of at least 2 carbon atoms and a total of up to 11 carbon atoms, and may also include one or more heteroatoms selected from the group consisting of O, S, and N.

For certain embodiments, e.g., of a pharmaceutical composition comprising a compound of Formula I, II, IIa, III, IV, IVa, V, or Va, or a pharmaceutically acceptable

salt thereof, or of a compound or salt of Formula IIa, III, IVa, or Va, or of any one of the above embodiments which includes an -OH group in a Formula, for example when $R_2$ is $-CH_2OH$, the –OH group can be replaced by an $-O-G_2$ group, to form prodrugs. In such embodiments, $G_2$ is selected from the group consisting of $-X_2-C(O)-R''$, α-aminoacyl, α-aminoacyl-α-aminoacyl, $-X_2-C(O)-O-R''$, $-C(O)-N(R''')R''$; and $-S(O)_2-R''$. For certain of these embodiments, $X_2$ is selected from the group consisting of a bond; $-CH_2-O-$; $-CH(CH_3)-O-$; $-C(CH_3)_2-O-$; and, in the case of $-X_2-C(O)-O-R''$, $-CH_2-NH-$. Preferrably, R'' and R''' are independently selected from the group consisting of $C_{1-10}$ alkyl, $C_{3-7}$ cycloalkyl, phenyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, $C_{1-6}$ alkyl, $C_{1-4}$ alkoxy, aryl, heteroaryl, aryl-$C_{1-4}$ alkylenyl, heteroaryl-$C_{1-4}$ alkylenyl, halo-$C_{1-4}$ alkylenyl, halo-$C_{1-4}$ alkoxy, $-O-C(O)-CH_3$, $-C(O)-O-CH_3$, $-C(O)-NH_2$, $-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$, with the proviso that R''' can also be hydrogen. Preferrably, α-aminoacyl is an α-aminoacyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from a naturally occuring amino acid selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from an amino acid found in proteins, wherein the the amino acid is selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments where $G_2$ is present, $G_2$ is selected from the group consisting of α-amino-$C_{2-5}$ alkanoyl, $C_{2-6}$ alkanoyl, $C_{1-6}$ alkoxycarbonyl, and $C_{1-6}$ alkylcarbamoyl.

For certain embodiments, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of the above embodiments of Formulas IIa, IVa, or Va in combination with a pharmaceutically acceptable carrier.

For certain embodiments, the present invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of any one of the above embodiments of a pharmaceutical composition or a compound or salt of any one of the above embodiments of Formulas I, II, IIa, III, IV, IVa, V, or Va to the animal. For certain of these embodiments, the cytokine is selected from the group consisting of IFN-α, TNF-α, IL-6, IL-10, and IL-12. For certain of these embodiments, the cytokine is IFN-α or TNF-α. For certain of these embodiments, the cytokine is IFN-α.

For certain embodiments, the present invention provides a method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of any one of the above embodiments of a pharmaceutical composition or a compound or salt of any one of the above embodiments of Formulas I, II, IIa, III, IV, IVa, V, or Va to the animal.

For certain embodiments, the present invention provides method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of any one of the above embodiments of a pharmaceutical composition or a compound or salt of any one of any one of the above embodiments of Formulas I, II, IIa, III, IV, IVa, V, or Va to the animal.

As used herein, the terms "alkyl", "alkenyl", "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "-alkylene-", "alkenylene", "-alkenylene-", "alkynylene", and "-alkynylene-" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms "alkylenyl", "alkenylenyl", and "alkynylenyl" are used when "alkylene", "alkenylene", and "alkynylene", respectively, are

substituted. For example, an arylalkylenyl group comprises an "alkylene" moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of alkyl groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2 to 12 carbon atoms, 1 to 3 rings, 1 to 4 heteroatoms, and O, S, and/or N as the heteroatoms. Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2 to 12 carbon atoms, 1 to 3 rings, 1 to 4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

The term "heterocyclyl" includes bicylic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can

include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene", "heteroarylene", and "heterocyclylene" are the divalent forms of the "aryl", "heteroaryl", and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene", "heteroarylene," and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

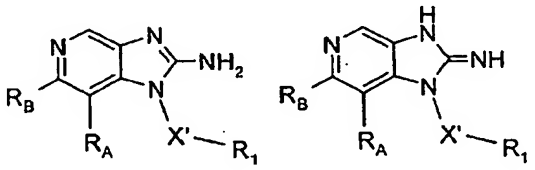
When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-N(R_9)-$ each $R_9$ group is independently selected. In another example, when more than one Y group is present, each Y group is independently selected. In a further example, when more than one $-N(R_8)-Q-R_4$ group is present (e.g., more than one $-Y-R_4$ group is present, and both contain a $-N(R_8)-Q-$ group) each $R_8$ group is independently selected, each Q group is independently selected, and each $R_4$ group is independently selected.

The invention is inclusive of the compounds described herein (including intermediates) in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, prodrugs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms described above. The transformation may occur by vaious mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W.

Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

Compounds (including intermediates) of the present invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies, which are interconvertible via a low energy barrier. For example, proton tautomers (prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. When compounds or compounds in compositions of the present invention have an amino group for the $R_2$ group, proton migration between the nitrogen atom of the amino group and the nitrogen atom at the 3-position may occur. For example, the following Formulas $I_a$ and $I_b$ are tautomeric forms of each other:



$I_a$ $I_b$

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritsky, Otto Meth-Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v. 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds of the invention. Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional methods well known to those skilled in the art.

In the preparation of compounds of the invention it may sometimes be necessary to protect a particular functionality while reacting other functional groups on an intermediate. The need for such protection will vary depending on the nature of the particular functional group and the conditions of the reaction step. Suitable amino protecting groups include acetyl, trifluoroacetyl, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl, and 9-fluorenylmethoxycarbonyl (Fmoc). Suitable hydroxy protecting groups include acetyl and silyl groups such as the *tert*-butyl dimethylsilyl group. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, USA, 1991.

Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention, as well as various intermediates related thereto. Such techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

For some embodiments of the invention, compounds can be prepared according to Reaction Scheme I wherein R, $R_1$, $R_2$, X‴, and n are as defined above and E is carbon (imidazoquinolines) or nitrogen (imidazonaphthyridines).

In step (1) of Reaction Scheme I, a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XX is reacted with an amine of Formula $R_1$-X‴-$NH_2$ to provide a compound of Formula XXI. The reaction can be carried out by adding the amine to a solution of a compound of Formula XX in a suitable solvent such as anhydrous

tetrahydrofuran in the presence of a base such as triethylamine. The reaction can be run at ambient temperature, at a sub-ambient temperature such as, for example 0 °C, or at an elevated temperature such as, for example, 45 °C. Many compounds of Formula XX are known or can be prepared using known synthetic methods, see for example, U.S. Patent Nos. 4,689,338 (Gerster), 5,268,376 (Gerster), 5,389,640 (Gerster et al.), 6,194,425 (Gerster, et al.), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.), 6,660,747 (Crooks et al.), 6,683,088 (Crooks et al.), 6,656,938 (Crooks et al.), and U.S. Patent Application Publication No. US 2004/0147543 (Hays et al.). Some amines of Formula $R_1$-X'''-$NH_2$ are commercially available; others can be prepared using known synthetic methods.

In step (2) of Reaction Scheme I, a compound of Formula XXI is reduced to provide a compound of Formula XXII. The reduction can be carried out using a conventional heterogeneous hydrogenation catalyst such as platinum on carbon. The reaction can be conveniently carried out on a Parr apparatus in a suitable solvent such as acetonitrile, toluene, ethanol, methanol, and/or isopropanol.

Other reduction processes may be used for the reduction in step (2). For example, an aqueous solution of sodium dithionite can be added to a solution or suspension of the compound of Formula XXI in a suitable solvent such as ethanol or isopropanol. The reaction can be carried out at an elevated temperature, for example, at reflux, or at ambient temperature.

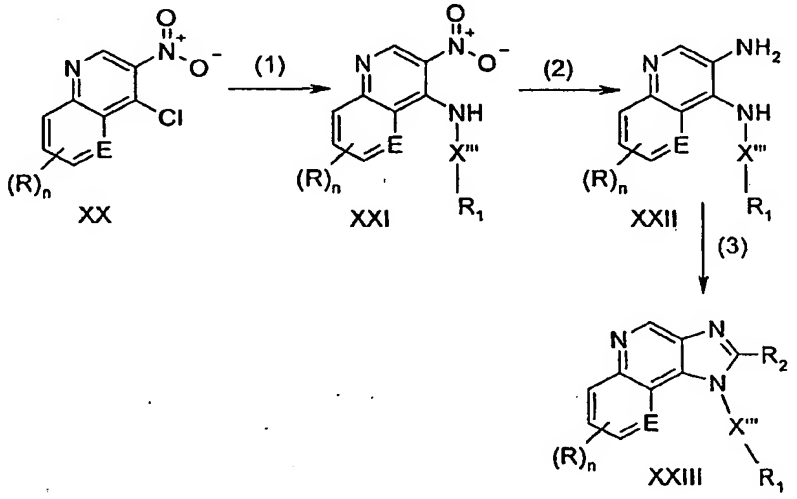
For step (3) of Reaction Scheme I, a compound of Formula XXII is (i) reacted with an acyl halide of Formula $R_2C(O)Cl$ or $R_2C(O)Br$ and then (ii) cyclized to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII. In part (i) the acyl halide is added to a solution of a compound of Formula XXII in a suitable solvent such as acetonitrile or anhydrous dichloromethane optionally in the presence of a base such as triethylamine. The reaction can be run at a reduced temperature, for example, 0° C, or at ambient temperature. In part (ii) the product of part (i) is heated in an alcoholic solvent in the presence of a base. For example, the product of part (i) is refluxed in ethanol in the presence of excess triethylamine or is heated with methanolic ammonia.

Alternatively, step (3) can be carried out by reacting a compound of Formula XXII with a carboxylic acid or an equivalent thereof. Suitable equivalents to carboxylic acid include orthoesters and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is

selected such that it will provide the desired $R_2$ substituent in a compound of Formula XXIII. For example, triethyl orthovalerate will provide a compound where $R_2$ is butyl. The reaction can be run in the absence of solvent or in an inert solvent such as anhydrous toluene. The reaction is run at an elevated temperature. Optionally a catalyst such as pyridine hydrochloride can be utilized.

Alternatively, when $R_2$ is $-NH_2$, the reaction can be carried out by reacting a compound of Formula XXII with cyanogen bromide in a suitable solvent such as ethanol. The reaction can be run at an elevated temperature, for example, at reflux.

Reaction Scheme I




For some embodiments of the invention, compounds can be prepared according to Reaction Scheme II wherein R, $R_1$, $R_2$, E, X''', and m are as defined above and $R_{3d}$ is as defined below. 1*H*-Imidazo[4,5-*c*]quinolines or 1*H*-imidazo[4,5-*c*][1,5]naphthyridines of Formula XXIV can be prepared according to Reaction Scheme I.

Compounds of Formula XXIV can undergo known palladium-catalyzed coupling reactions such as the Suzuki coupling and the Heck reaction. For example, a compound of Formula XXIV undergoes Suzuki coupling with a boronic acid of Formula $R_{3d}$-$B(OH)_2$, an anhydride thereof, or a boronic acid ester of Formula $R_{3d}$-B(O-alkyl)$_2$; wherein $R_{3d}$ is $-R_{4b}$, $-X_a$-$R_4$, $-X_b$-Y-$R_4$, or $-X_b$-$R_5$; where $X_a$ is alkenylene; $X_b$ is arylene, heteroarylene, and alkenylene interrupted or terminated by arylene or heteroarylene; $R_{4b}$ is aryl or heteroaryl

where the aryl or heteroaryl groups can be unsubstituted or substituted as defined in $R_4$ above; and $R_4$, $R_5$, and Y are as defined above; to provide a compound of Formula XXV. Numerous boronic acids of Formula $R_{3d}$-$B(OH)_2$, anhydrides thereof, and boronic acid esters of Formula $R_{3d}$-B(O-alkyl)$_2$ are commercially available; others can be readily prepared using known synthetic methods.

The Heck reaction can also be used in Reaction Scheme II to provide compounds of Formula XXV, wherein $R_{3d}$ is -$X_a$-$R_{4b}$ and -$X_a$-Y-$R_4$. The Heck reaction is carried out by coupling a compound of Formula XXIV with a compound of the Formula $H_2C$=C(H)-$R_{4b}$ or $H_2C$=C(H)-Y-$R_4$. Several of these vinyl-substituted compounds are commercially available; others can be prepared by known methods. The Suzuki coupling and Heck reaction can be carried out according to any of the methods described in U. S. Patent Application Publication No. 2004/0147543 (Hays et al.).

Compounds of Formula XXV, wherein $R_{3d}$ is -$X_c$-$R_4$, $X_c$ is alkynylene, and $R_4$ is as defined above, can also be prepared by palladium catalyzed coupling reactions such as the Stille coupling or Sonogashira coupling. These reactions are carried out by coupling a compound of Formula XXIV with a compound of the Formula (alkyl)$_3$Sn-C≡C-$R_4$, (alkyl)$_3$Si-C≡C-$R_4$, or H-C≡C-$R_4$.

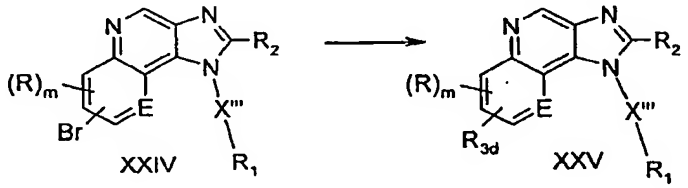
Compounds of Formula XXV prepared as described above by palladium-mediated coupling reactions, wherein $R_{3d}$ is -$X_a$-$R_4$, -$X_a$-Y-$R_4$, -$X_{b2}$-Y-$R_4$, -$X_{b2}$-$R_5$, or -$X_c$-$R_4$, where $X_{b2}$ is alkenylene interrupted or terminated by arylene or heteroarylene, and $X_a$, $X_c$, Y, $R_4$, and $R_5$ are as defined above, can undergo reduction of the alkenylene or alkynylene group present to provide compounds of Formula XXV wherein $R_{3d}$ is -$X_d$-$R_4$, -$X_d$-Y-$R_4$, -$X_e$-Y-$R_4$, or -$X_e$-$R_5$, where $X_d$ is alkylene; $X_e$ is alkylene interrupted or terminated by arylene or heteroarylene; and $R_4$, $R_5$, and Y are as defined above. The reduction can be carried out by hydrogenation according to the methods described in U. S. Patent Application Publication No. 2004/0147543 (Hays et al.).

A copper-mediated coupling reaction can be used to prepare compounds of Formula XXV, wherein $R_{3d}$ is -NH-C($R_6$)-$R_4$, -NH-$SO_2$-$R_4$. The reaction can be carried out by combining a compound of Formula XXIV and an amide or sulfonamide of formula -NH-C($R_6$)-$R_4$ or -NH-$SO_2$-$R_4$ in the presence of copper (I) iodide, potassium phosphate, and racemic *trans*-1,2-diaminocyclohexane in a suitable solvent such as 1,4-dioxane. The reaction can be carried out at an elevated temperature such as 110 °C. Many amides and

sulfonamides of these formulas are commercially available; others can be made by conventional methods. These reaction conditions can also be used to couple a compound of Formula XXIV with a wide variety of nitrogen-containing heterocycles to provide a compound of Formula XXV wherein $R_{3d}$ is -heterocyclyl, -heterocyclylene-$R_4$, or -heterocyclylene-Y-$R_4$, wherein the heterocyclyl or heterocyclylene is attached to the quinoline or naphthyridine ring through a nitrogen atom.

In addition, certain of these compounds of Formula XXV wherein $R_{3d}$ is -heterocyclyl, -heterocyclylene-$R_4$, or -heterocyclylene-Y-$R_4$, wherein the heterocyclyl or heterocyclylene is attached to the quinoline or naphthyridine ring through a nitrogen atom, can be prepared using a palladium-mediated coupling, which is conveniently carried out by combining a compound of the Formula XXIV and the nitrogen-containing heterocyclyl compound in the presence of tris(dibenzylideneacetone)dipalladium, (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, sodium *tert*-butoxide, and a suitable solvent such as toluene. The reaction can be carried out at an elevated temperature such as 80 °C. The synthetic methods described in International Publication No. WO 05/123080 (Merrill *et al.*) can also be used. These reaction conditions can also be used to prepare compounds wherein $R_{3d}$ is -NH-$R_4$.

Reaction Scheme II




For some embodiments of the invention, compounds can be prepared according to Reaction Scheme III wherein R, $R_1$, $R_2$, E, X''', and m are as defined above, Bn is benzyl, and $R_{3e}$ is as defined below.

In step (1) of Reaction Scheme III, a benzyloxyaniline or benzyloxyaminopyridine of Formula XXVI is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide an imine of Formula XXVII. The reaction can be carried out by adding a solution of a compound of

Formula XXVI to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature such as 45 °C. Many anilines and aminopyridines of Formula XXVI are commercially available; others can be prepared by known synthetic methods. For example, benzyloxypyridines of Formula XXVI can be prepared using the method of Holladay et al., *Biorg. Med. Chem. Lett.*, *8*, pp. 2797-2802, (1998).

In step (2) of Reaction Scheme III, an imine of Formula XXVII undergoes thermolysis and cyclization to provide a compound of Formula XXVIII. The reaction is conveniently carried out in a medium such as DOWTHERM A heat transfer fluid at a temperature in the range of 200 to 250 °C.

In step (3) of Reaction Scheme III, a compound of Formula XXVIII is nitrated under conventional nitration conditions to provide a benzyloxy-3-nitroquinolin-4-ol or benzyloxy-3-nitro[1,5]naphthyridin-4-ol of Formula XXIX. The reaction is conveniently carried out by adding nitric acid to the compound of Formula XXVIII in a suitable solvent such as propionic acid and heating the mixture at an elevated temperature such as 125 °C.

In step (4) of Reaction Scheme III, a benzyloxy-3-nitroquinolin-4-ol or benzyloxy-3-nitro[1,5]naphthyridin-4-ol of Formula XXIX is chlorinated using conventional chlorination chemistry to provide a benzyloxy-4-chloro-3-nitroquinoline or benzyloxy-4-chloro-3-nitro[1,5]naphthyridine of Formula XXX. The reaction is conveniently carried out by treating the compound of Formula XXIX with phosphorous oxychloride in a suitable solvent such as DMF. The reaction can be carried out at an elevated temperature such as 100 °C.

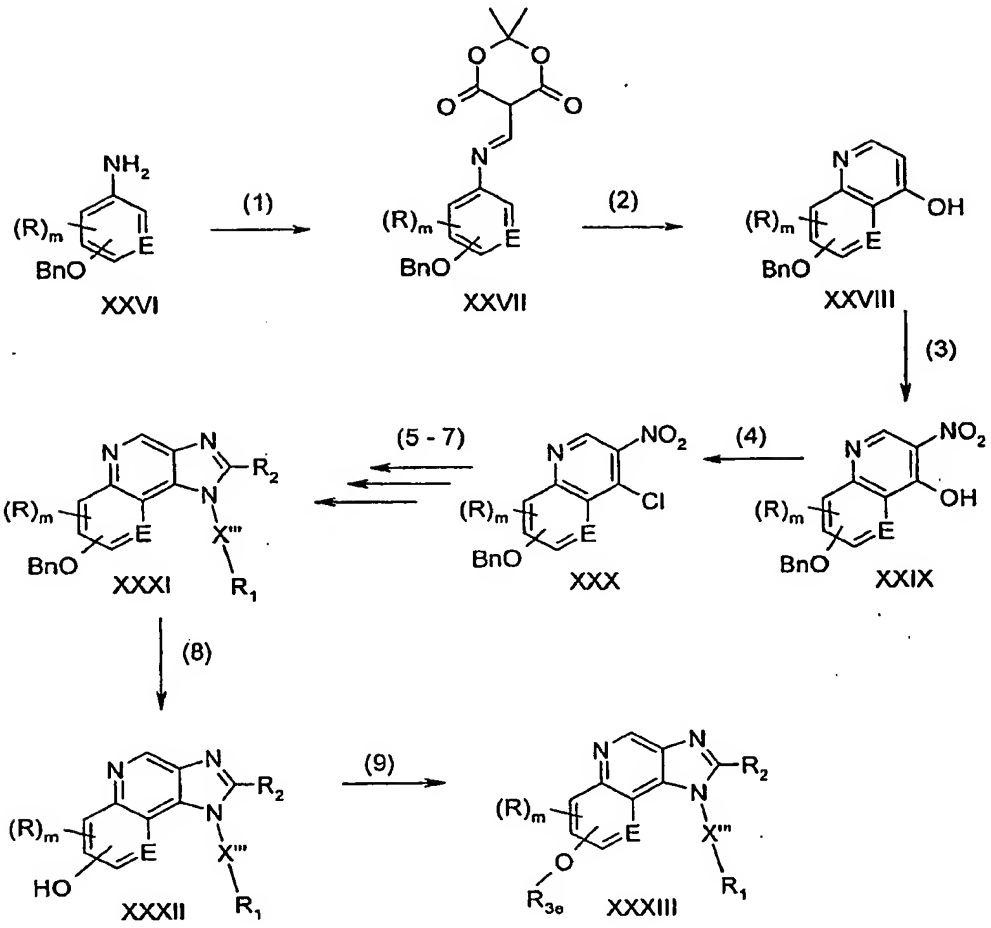
Steps (5), (6), and (7) of Reaction Scheme III can be carried out according to the methods of steps (1), (2), and (3), respectively, of Reaction Scheme I.

In step (8) of Reaction Scheme III, the benzyl group of a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline or benzyloxy-1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXXI is cleaved to provide a 1*H*-imidazo[4,5-*c*]quinolinol or 1*H*-imidazo[4,5-*c*][1,5]naphthyridinol of Formula XXXII. The cleavage can be carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium on carbon in a solvent such as ethanol. Alternatively, the reaction can be carried out by transfer hydrogenation in the presence of a suitable hydrogenation catalyst. The transfer hydrogenation can be carried out by adding ammonium formate to a solution

of a compound of Formula XXXI in a suitable solvent such as ethanol in the presence of a catalyst such as palladium on carbon. The reaction is carried out at an elevated temperature, for example, the reflux temperature of the solvent.

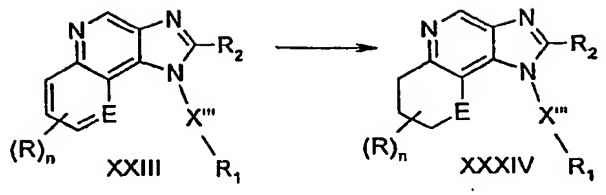
In step (9) of Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinolinol or 1*H*-imidazo[4,5-*c*][1,5]naphthyridinol of Formula XXXII is converted to an ether-substituted 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXXIII using a Williamson-type ether synthesis. The reaction is carried out by treating a compound of Formula XXXII with an aryl, alkyl, or arylalkylenyl halide of Formula halide-$R_{4b}$, halide-alkylene-$R_4$, halide-alkylene-Y-$R_4$, or halide-alkylene-$R_5$ in the presence of a base. The reaction can be carried out by combining the halide with a compound of Formula XXXII in a solvent such as DMF in the presence of a suitable base such as cesium carbonate. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 65 °C or 85 °C. Numerous alkyl, arylalkylenyl, and aryl halides of these formulas are commercially available, including substituted benzyl bromides and chlorides, substituted or unsubstituted alkyl or arylalkylenyl bromides and chlorides, and substituted fluorobenzenes. Other halides of these formulas can be prepared using conventional synthetic methods. The methods described in International Publication Nos. WO2005/020999 (Lindstrom *et al.)* and WO2005/032484 (Lindstrom *et al.)* can be used.

Reaction Scheme III




For some embodiments of the invention, compounds can be prepared according to Reaction Scheme IV wherein R, $R_1$, $R_2$, E, X''', and n are as defined above. In Reaction Scheme IV a 1*H*-Imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXIII is reduced to provide a compound of Formula XXXIV. The reaction can be carried out by suspending or dissolving a compound of Formula XXIII in trifluoroacetic acid, adding platinum (IV) oxide, and hydrogenating. The reaction can be carried out on a Parr apparatus.

Reaction Scheme IV

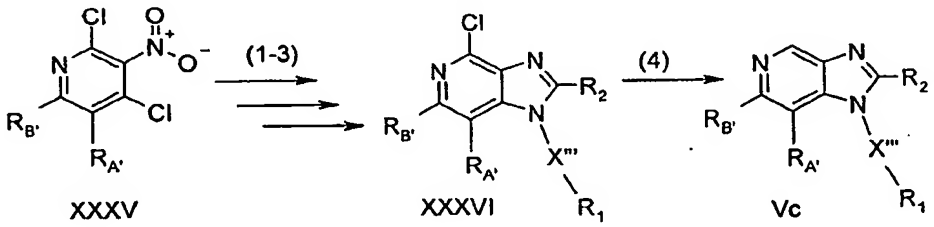



For some embodiments of the invention, compounds can be prepared according to Reaction Scheme V wherein $R_1$, $R_2$, $R_{A'}$, $R_{B'}$, and X''' are as defined above.

In steps (1) through (3) of Reaction Scheme V, a 2,4-dichloro-3-nitropyridine of Formula XXXV is converted to a 4-chloro-1*H*-imidazo[4,5-*c*]pyridine of Formula XXXVI. The steps can be carried out according to the general methods of steps (1) through (3) of Reaction Scheme I. 2,4-Dichloro-3-nitropyridines of Formula XXXV are known or can be prepared using known synthetic methods, see for example, U.S. Patent No. 6,525,064 (Dellaria, *et al.)* and the references cited therein.

In step (4) of Reaction Scheme V, the chloro group is removed from a 4-chloro-1*H*-imidazo[4,5-*c*]pyridine of Formula XXXVI to provide a 1*H*-imidazo[4,5-*c*]pyridine of Formula Vc. The reaction can be carried out using ammonium formate and a heterogeneous catalyst such as palladium on carbon in a solvent mixture comprised of ethanol and methanol. The reaction is carried out at an elevated temperature, such as for example, the reflux temperature of the solvent system.

Reaction Scheme V




For some embodiments of the invention, compounds can be prepared according to Reaction Scheme VI wherein R, $R_1$, $R_2$, E, and n are as defined above.

In step (1) of Reaction Scheme VI, a 1*H*-Imidazo[4,5-*c*]quinolin-1-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-amine of Formula XXXVII is reacted with a ketone of the Formula $R_1$=O under acidic conditions to provide a hydrazone of Formula XXXVIII. The reaction can be carried out by adding the ketone to a solution of a compound of Formula XXXVII in a suitable solvent such as acetonitrile in the presence of an acid such as glacial acetic acid. The reaction is run at an elevated temperature, such as for example, at 110 °C. Compounds of Formula XXXVII are known or can be prepared using known synthetic methods, see for example, U.S. Patent Application Publication No. 2005/0054640 (Griesgraber *et al.*) and International Publication No. WO 06/026760 (Stoermer *et al.*) and the references cited therein.

In step (2) of Reaction Scheme VI, a hydrazone of Formula XXXVIII is reduced to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXXIX. The reaction can be carried out by adding sodium borohydride to a solution of a compound of Formula XXXVIII in a suitable solvent such as methanol. The reaction can be run at ambient temperature or at a sub-ambient temperature, such as for example, 0 °C.

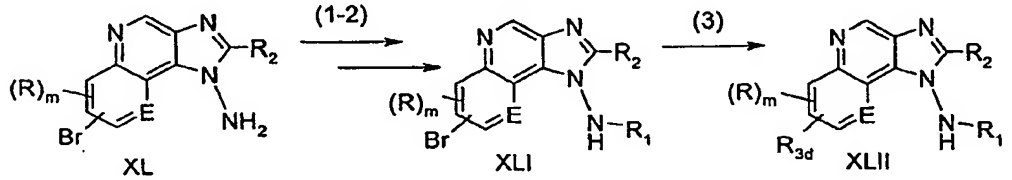
Reaction Scheme VI


For some embodiments of the invention, compounds can be prepared according to Reaction Scheme VII wherein R, $R_1$, $R_2$, $R_{3d}$, E, and m are as defined above.

In steps (1) and (2) of Reaction Scheme VII, a bromo substituted 1*H*-imidazo[4,5-*c*]quinolin-1-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-amine of Formula XL is converted to a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLI using the methods of steps (1) and (2) of Reaction Scheme VI. Compounds of Formula XL are known or can be prepared using known synthetic methods, see for example U.S. Patent Application Publication No. 2005/0054640 (Griesgraber *et al.*) and International Publication No. WO 06/026760 (Stoermer *et al.*) and the references cited therein.

In step (3) of Reaction Scheme VII a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLI is converted to a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLII using the methods described in Reaction Scheme II.

Reaction Scheme VII

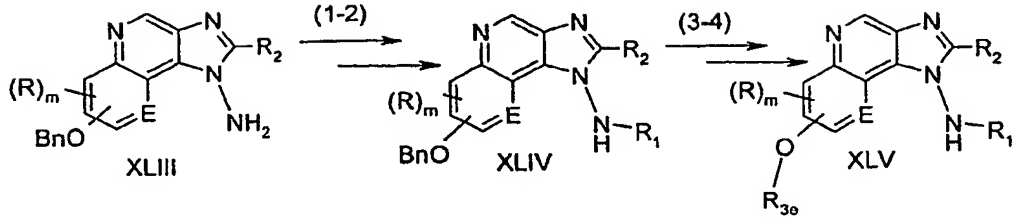



For some embodiments of the invention, compounds can be prepared according to Reaction Scheme VIII wherein R, $R_1$, $R_2$, $R_{3c}$, Bn, E, and m are as defined above.

In steps (1) and (2) of Reaction Scheme VIII, a benzyloxy substituted 1*H*-imidazo[4,5-*c*]quinolin-1-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-amine of Formula XLIII is converted to a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLIV using the methods of steps (1) and (2) of Reaction Scheme VI. Compounds of Formula XLIII are known or can be prepared using known synthetic methods, see for example, U.S. Patent Application Publication No. 2005/0054640 (Griesgraber *et al.*) and International Publication No. WO 06/026760 (Stoermer *et al.*) and the references cited therein.

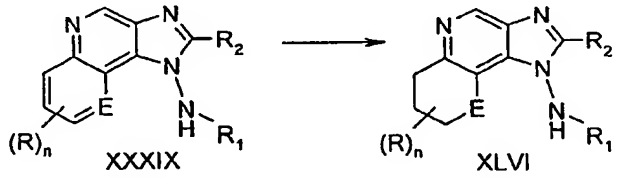
In steps (3) and (4) of Reaction Scheme VIII a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLIV is converted to a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLV using the methods described in steps (8) and (9) respectively of Reaction Scheme III.

Reaction Scheme VIII




For some embodiments of the invention, compounds can be prepared according to Reaction Scheme IX wherein R, $R_1$, $R_2$, E, and n are as defined above. In Reaction Scheme IX, 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXXIX is reduced to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLVI. The reduction can be carried out as described in Reaction Scheme IV.

Reaction Scheme IX

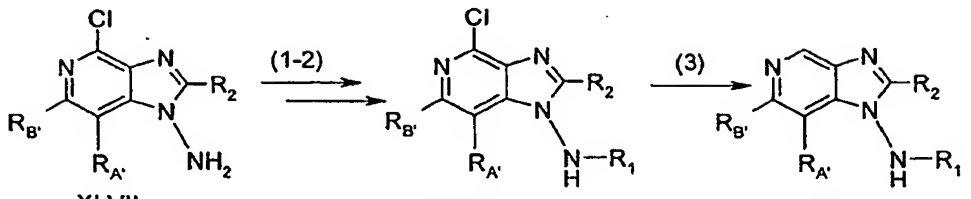



For some embodiments of the invention, compounds can be prepared according to Reaction Scheme X wherein $R_1$, $R_2$, $R_{A'}$, and $R_{B'}$ are as defined above.

In steps (1) and (2) of Reaction Scheme X, a 4-chloro-1*H*-imidazo[4,5-*c*]pyridin-1-amine of Formula XLVII is converted to a 4-chloro-1*H*-imidazo[4,5-*c*]pyridin-1-amine of Formula XLVIII using the methods of steps (1) and (2) of Reaction Scheme VI. Compounds of Formula XLVII are known or can be prepared using known synthetic methods, see for example, International Publication No. WO 06/026760 (Stoermer *et al.*) and the references cited therein.

In step (3) of Reaction Scheme X, the chloro group is removed from a 4-chloro-1*H*-imidazo[4,5-*c*]pyridin-1-amine of Formula XLVIII to provide a 1*H*-imidazo[4,5-*c*]pyridin-1-amine of Formula Vd. The reaction can be carried out as described in step (4) of Reaction Scheme V.

Reaction Scheme X



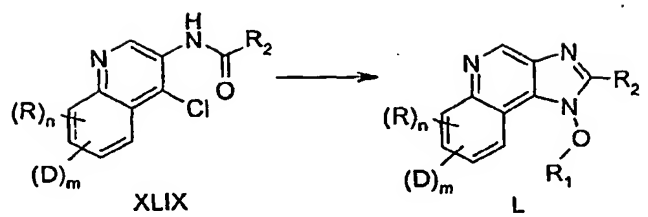

XLVII XLVIII Vd

For some embodiments of the invention, compounds can be prepared according to Reaction Scheme XI wherein R, $R_1$, $R_2$, E, m, and n are as defined above and D is bromo or benzyloxy.

In reaction Scheme XI an *N*-(4-chloroquinolin-3-yl)amide or *N*-(4-chloro[1,5]napthyridin-3-yl)amide of Formula XLIX is reacted with a hydroxylamine hydrochloride of Formula $R_1ONH_2$•HCl and cyclized to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula L. The reaction can be carried out by adding the hydroxylamine hydrochloride to a solution of a compound of Formula XLIX in an alcoholic solvent such as ethanol. The reaction can be carried out at an elevated temperature, such as for example, the reflux temperature of the solvent. *N*-(4-Chloroquinolin-3-yl)amides and *N*-(4-chloro[1,5]napthyridin-3-yl)amides of Formula XLIX are known or can be prepared using known synthetic methods, see for example, International Publication No. WO 06/028962 (Krepski *et al.*).

Compounds of Formula L wherein m is 1 and D is bromo can be further elaborated using the general methods described in Reaction Scheme II. Compounds of Formula I wherein m is 1 and D is benzyloxy can be further elaborated using the general methods described in Reaction Scheme III.

Reaction Scheme XI




For some embodiments of the invention, compounds can be prepared according to Reaction Scheme XII wherein R, $R_1$, $R_2$, Bn, E, and n are as defined above.

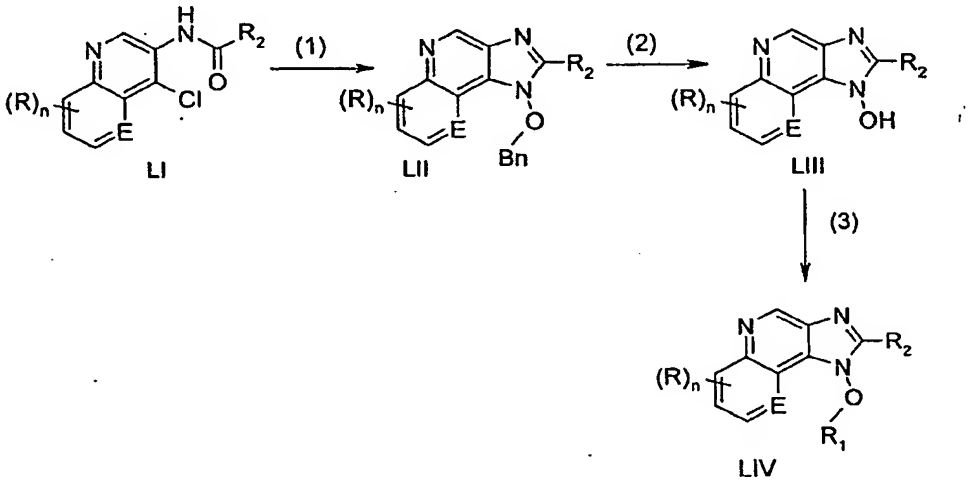
In step (1) of Reaction Scheme XII, an *N*-(4-chloroquinolin-3-yl)amide or *N*-(4-chloro[1,5]napthyridin-3-yl)amide of Formula LI is reacted with *O*-benzylhydroxylamine hydrochloride and cyclized to provide a 1-benzylox-1*H*-imidazo[4,5-*c*]quinoline or 1-benzyloxy-1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LII. The reaction can be carried out by adding the *O*-benzylhydroxylamine hydrochloride to a solution of a compound of Formula LI in an alcoholic solvent such as isopropanol. The reaction can be carried out at an elevated temperature, such as for example, the reflux temperature of the solvent. *N*-(4-Chloroquinolin-3-yl)amides and *N*-(4-chloro[1,5]napthyridin-3-yl)amides of Formula LI are known or can be prepared using known synthetic methods, see for example, International Publication No. WO 06/028962 (Krepski *et al.*).

In step (2) of Reaction Scheme XII, the benzyl group of a 1-benzyloxy-1*H*-imidazo[4,5-*c*]quinoline or 1-benzyloxy-1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LII is cleaved to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-ol or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-ol of Formula LIII. The cleavage can be carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium on carbon in a solvent such as ethanol. Alternatively, the reaction can be carried out by transfer hydrogenation in the presence of a suitable hydrogenation catalyst. The transfer hydrogenation can be carried out by adding ammonium formate to a solution of a compound of Formula LII in a suitable solvent such as ethanol in the presence of a catalyst such as palladium on carbon. The reaction is carried out at an elevated temperature, for example, the reflux temperature of the solvent.

In step (3) of Reaction Scheme XII, a 1*H*-imidazo[4,5-*c*]quinolin-1-ol or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-ol of Formula LIII is converted to an ether-substituted

1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LIV. The reaction can carried out by treating a compound of Formula LIII with a halide of Formula halide-$R_1$ in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction can be carried out by heating a mixture of the halide, a compound of Formula LIII, and the DBU in a sealed pressure vessel at an elevated temperature, for example 120 °C. Some halides of the Formula halide-$R_1$ commercially available; others can be prepared using known synthetic methods.

Reaction Scheme XII




For some embodiments of the invention, compounds can be prepared according to Reaction Scheme XIII wherein R, $R_1$, $R_2$, Bn, and n are as defined above.

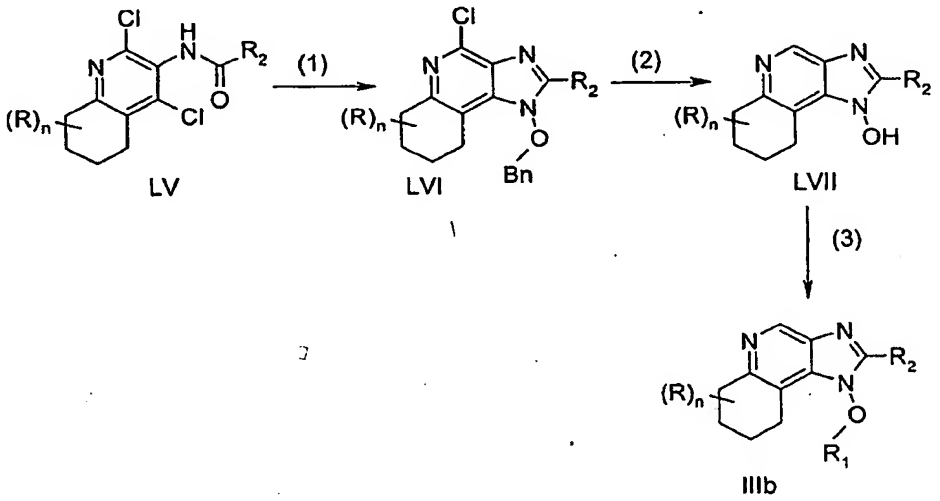
In step (1) of Reaction Scheme XIII, an *N*-(4-chloro-5,6,7,8-tetrahydroquinolin-3-yl)amide of Formula LV is reacted with *O*-benzylhydroxylamine hydrochloride and cyclized to provide a 1-benzyloxy-4-chloro-5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline of Formula LVI. The reaction can be carried out as described in step (1) of Reaction Scheme XII. *N*-(4-Chloro-5,6,7,8-tetrahydroquinolin-3-yl)amides of Formula LV are known or can be prepared using known synthetic methods, see for example, International Publication No. WO 06/028962 (Krepski *et al.*).

In step (2) of Reaction Scheme XIII, both the benzyl group and the chloro group of a 1-benzyloxy-4-chloro-5,6,7,8-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline are cleaved to

provide a 1*H*-imidazo[4,5-*c*]quinolin-1-ol of Formula LVII. The cleavage can be carried out as described in step (2) of Reaction Scheme XII.

In step (3) of Reaction Scheme XIII, a 1*H*-imidazo[4,5-*c*]quinolin-1-ol of Formula LVII is converted to an ether-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula IIIb using the method described in step (3) of Reaction Scheme XII.

Reaction Scheme XIII



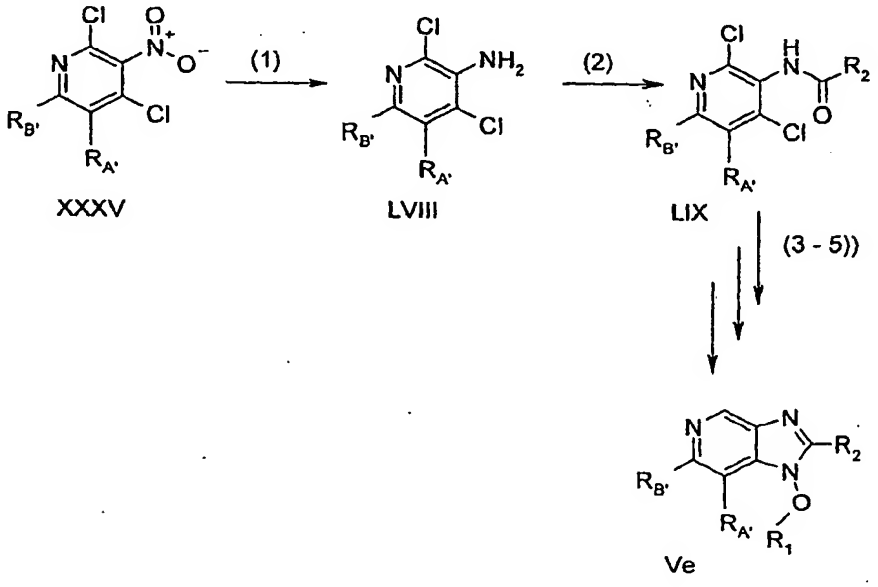

For some embodiments of the invention, compounds can be prepared according to Reaction Scheme XIV wherein $R_{A'}$, $R_{B'}$, $R_1$, and $R_2$ are as defined above.

In step (1) of Reaction Scheme XIV, a 2,4-dichloro-3-nitropyridine of Formula XXXV is reduced to provide a 2,4-dichloropyridin-3-amine of Formula LVIII. The reduction can be carried out using the methods described in step (2) of Reaction Scheme I.

In step (2) of Reaction Scheme XIV, a 2,4-dichloropyridin-3-amine of Formula LVIII is reacted with an acyl halide of Formula $R_2C(O)Cl$ or $R_2C(O)Br$ to provide an *N*-(2,4-dichloropyridin-3-yl)amide of Formula LIX. The reaction can be carried out by adding the acyl halide to a solution of the 2,4-dichloropyridin-3-amine of Formula LVIII in a suitable solvent such anhydrous dichloromethane optionally in the presence of a base such as triethylamine. The reaction can be run at a reduced temperature, for example, 0 °C, or at ambient temperature.

In steps (3), (4), and (5) of Reaction Scheme XIV, an *N*-(2,4-dichloropyridin-3-yl)amide of Formula LIX is converted to an ether substituted 1*H*-imidazo[4,5-*c*]pyridine of Formula Ve using the methods described in steps (1), (2), and (3) respectively of Reaction Scheme XIII.

Reaction Scheme XIV




Compounds useful in the compositions of the invention and compounds of the invention can also be prepared using variations in the synthetic routes shown in Reaction Schemes I through XI that would be apparent to one of skill in the art. Compounds useful in the compositions of the invention and compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect,

such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. The exact amount of compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen.

In some embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject.

In other embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of, for example, from about 0.01 $mg/m^2$ to about 5.0 $mg/m^2$, computed according to the Dubois method, in which the body surface area of a subject ($m^2$) is computed using the subject's body weight: $m^2 = (wt\ kg^{0.425} \times height\ cm^{0.725}) \times 0.007184$, although in some embodiments the methods may be performed by administering a compound or salt or composition in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound to provide a dose of from about 0.1 $mg/m^2$ to about 2.0 $mg/m^2$ to the subject, for example, a dose of from about 0.4 $mg/m^2$ to about 1.2 $mg/m^2$.

A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like. These dosage forms can be prepared with conventional pharmaceutically acceptable carriers and additives using conventional methods, which generally include the step of bringing the active ingredient into association with the carrier. In general, the compositions may be prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into the desired dosage form.

The pharmaceutically acceptable carrier may be a solid or a liquid or a gas that has been compressed to form a liquid. Suitable pharmaceutical carriers for use in the present pharmaceutical formulations are known. The carrier may take a wide variety of forms, depending on the form of preparation desired for administration, for example, such as

systemic administration (including but not limited to oral, parenteral, intravenous, or nasal) and topical administration.

In preparing the pharmaceutical compositions in oral dosage form, any of the usual pharmaceutical carriers may be employed, such as, for example, water, glycols, oils, and alcohols in the case of oral liquid preparations (e.g., emulsions, suspensions, elixirs, solutions, syrups), and carriers such as, for example, starches, sugars (including lactose, sucrose, glucose, mannitol), silicic acid, methylcellulose, carboxymethylcellulose, alginates, pectin, dextrin, gelatin, polyvinylpyrrolidone, acacia, glycerol, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium carbonate, low melting waxes, cocoa butter, cetyl alcohol, glycerol monostearate, kaolin and bentonite clay, talc, calcium stearate, magnesium carbonate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof in the case of oral solid preparations (e.g., pills, granules, powders, capsules, tablets).

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding thereto suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents. Aqueous suspensions suitable for oral use can be made by dispersing the active component in finely divided form in water with viscous materials or thickening agents such as, for example, synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well known suspending agents.

In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. Oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers include water, aqueous solutions, such as saline (sotinic sodium chloride solution), Ringer's solution, dextrose solution, and Hanks' solution, ethanol, polyols (such as 1,3-butanediol, glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils such as, for example, olive oil, corn oil, cottonseed oil, sesame oil, and castor oil, synthetic mono- or di-glyceride oils, and organic esters such as ethyl oleate and isopropyl myristate. Proper fluidity can be maintained, for example, by the use of coating

materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like, Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms may be made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Pharamaceutical compositions for topical application may include the above liquid forms, as well as ointments, creams, lotions, aerosols, sprays, dusts, and powders, which are prepared by combining an active component according with conventional pharmaceutically acceptable carriers commonly used in topical, dry, liquid, cream, and aerosol formulations. Ointments and creams may, for example, be formulated with an

aqueous or oily base with the addition of suitable thickening and/or gelling agents. Such bases may include, for example, water and/or oil such as mineral oil, liquid petrolatum, white petrolatum, or a vegetable oil. Thickening agents, which may be used according to the nature of the base, include soft paraffin, aluminum stearate, cetostearyl alcohol, propylene glycol, polyethylene glycols, polyoxyethylene, polyoxypropylene, hydrogenated lanolin, beeswax, and the like. Alternatively, the active component can be formulated into suitable lotions or creams containing the active component suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, polysorbate 60, cetyl ester wax, cetostearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Administration of the pharmaceutical compositions and compounds and/or salts of the invention may be in the form of an aerosol, for example, for nasal or inhalation applications. The active component may be delivered in the form of an aerosol from a pressurized pack or nebulizer with the use of a suitable propellant such as, for example, carbon dioxide, air, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2-tetrafluoroethane, or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules or cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the active component and a suitable powder base such as lactose or starch.

The compounds and/or salts or compositions described herein may also be delivered in the form of transdermal patches, transmucosal patches, and the like. Matrix or reservoir type patches that are conventional in the art for transdermal or transmucosal delivery may be used for this purpose. Here the matrix, such as a pressure sensitive adhesive matrix, or the carrier in the reservoir act as the pharmaceutically acceptable carrier.

The compounds or salts described herein can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts described herein may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compositions and compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts or compositions are useful for modulating the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts or compositions described herein generally include interferon-α (IFN-α) and tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts or compositions useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt or composition may provide therapeutic treatment. Alternatively, the compound or salt or composition may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt or composition may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts described herein can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts described herein can also have an effect on the acquired immune response. For example, the production of the T helper type 1 ($T_H1$) cytokine IFN-γ may be induced indirectly and the production of the T helper type 2 ($T_H2$) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt or composition and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts or compositions identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such as chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to acute myeloid

leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) $T_H2$-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a compound or salt or composition identified herein may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts or compositions identified herein may be particularly helpful in individuals having compromised immune function. For example, compounds or salts or compositions may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of or a composition comprising a therapeutically effective amount of a compound or salt of

Formula I, II, IIa, III, IV, IVa, V, Va, any one of the embodiments described herein, or a combination thereof to the animal. An animal may also be vaccinated by administering an effective amount of a compound or salt of or a composition comprising an effective amount of a compound or salt of Formula I, II, IIa, III, IV, IVa, V, Va, any one of the embodiments described herein, or a combination thereof to the animal as a vaccine adjuvant. In one embodiment, there is provided a method of vaccinating an animal comprising administering an effective amount of a compound or salt or composition described herein to the animal as a vaccine adjuvant.

An amount of a compound or salt or composition effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 $mg/m^2$ to about 5.0 $mg/m^2$, (computed according to the Dubois method as described above) although in some embodiments the induction of cytokine biosynthesis may be performed by administering a compound or salt or composition in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or composition to provide a dose of from about 0.1 $mg/m^2$ to about 2.0 $mg/m^2$ to the subject, for example, a dose of from about 0.4 $mg/m^2$ to about 1.2 $mg/m^2$.

The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt or composition effective to treat a neoplastic condition is an amount that will cause a

reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 $mg/m^2$ to about 5.0 $mg/m^2$, (computed according to the Dubois method as described above) although in some embodiments either of these methods may be performed by administering a compound or salt or composition in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or composition to provide a dose of from about 0.1 $mg/m^2$ to about 2.0 $mg/m^2$ to the subject, for example, a dose of from about 0.4 $mg/m^2$ to about 1.2 $mg/m^2$.

In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

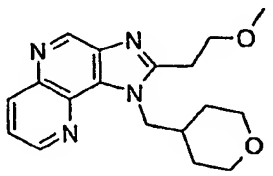
## EXAMPLES

In the examples below normal high performance flash chromatography (prep HPLC) was carried out using a COMBIFLASH system (an automated high-performance flash purification product available from Teledyne Isco, Inc., Lincoln, Nebraska, USA), a HORIZON HPFC system (an automated high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA) or an INTELLIFLASH Flash Chromatography System (an automated flash purification system available from AnaLogix, Inc, Burlington, Wisconsin, USA). The eluent used in each purification is given in the example. In some chromatographic separations, the solvent mixture 80/18/2 v/v/v chloroform/methanol/concentrated ammonium hydroxide (CMA) was used as the

polar component of the eluent. In these separations, CMA was mixed with chloroform in the indicated ratio.

Example 1

2-(2-Methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine



Part A

Phosphorous oxychloride (2.55 mL, 27.5 mmol) was added dropwise to a suspension of 4-hydroxy-3-nitro[1,5]naphthyridine (5 g, 26.1 mmol) in *N,N*-dimethylformamide (DMF, 30 mL). The resulting mixture was heated to 60 °C to dissolve all of the solids. The reaction was maintained at 60 °C for 10 minutes and then allowed to cool to ambient temperature. The solution was poured into ice water (150 mL) and then stirred for 1 hour. A solid was isolated by filtration, washed with water until the filtrate was neutral, and then dried under vacuum for 30 minutes to provide 4-chloro-3-nitro[1,5]naphthyridine. This material was combined with tetrahydrofuran (THF, 30 mL). A mixture of triethylamine (7.32 mL, 52.5 mmol) and 1-tetrahydro-2*H*-pyran-4-ylmethylamine hydrochloride (4.17 g, 27.5 mmol) in THF was added dropwise to the slurry. The reaction mixture was stirred overnight and then diluted with water. A solid was isolated by filtration and dried under vacuum to provide 6.8 g of 3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridin-4-amine.

Part B

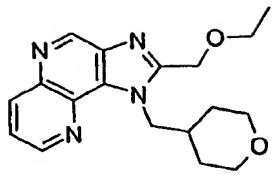
A mixture of 3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridin-4-amine (2.5 g, 8.67 mmol), 5% platinum on carbon (0.25 g), and acetonitrile (50 mL) was placed under hydrogen pressure on a Parr apparatus. When the reaction was complete, the mixture was filtered through a layer of CELITE filter agent. The filter cake was washed with acetonitrile. The filtrate was concentrated under reduced pressure to provide 2.37 g of crude $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine as a yellowish orange oil.

Part C

Under a nitrogen atmosphere a solution of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine (1.19 g, 4.61 mmol) in anhydrous dichloromethane (25 mL) was cooled in an ice bath for 10 minutes. Anhydrous triethylamine (1.0 mL, 6.92 mmol) was added in a single portion. 3-Methoxypropionyl chloride (0.55 mL, 5.07 mmol) was added dropwise and then the reaction mixture was allowed to stir at ambient temperature until analysis by liquid chromatography (LC) indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure to provide crude 3-methoxy-*N*-{4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino][1,5]naphthyridin-3-yl}propanamide as an orange solid. This material was suspended in anhydrous ethanol (25 mL) and combined with anhydrous triethylamine (2.25 mL, 16.14 mmol). The mixture was placed under a nitrogen atmosphere and heated at 110 °C over the weekend. The reaction mixture was concentrated under reduced pressure and then diluted with dichloromethane (100 mL). The organic layer was washed sequentially with water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-15% CMA in chloroform) to provide 0.82 g of an off-white solid. This material was suspended in cold methyl *tert*-butyl ether (MTBE, 10 mL), isolated by filtration, washed with cold MTBE, and then dried at 80 °C to provide 0.39 g of 2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as a light grey solid, mp 124-126 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.23 (s, 1H), 8.99 (dd, $J$ = 4.1, 1.6, 1H), 8.50 (dd, $J$ = 8.5, 1.6, 1H), 7.73 (dd, $J$ = 8.5, 4.7, 1H), 4.85 (d, $J$ = 6.3, 2H), 3.91 (t, $J$ = 6.7, 2H), 3.78 (dd, $J$ = 11.0, 3.2, 2H), 3.29 (s, 3H), 3.26 (t, $J$ = 6.7, 2H), 3.14 (td, $J$ = 11.3, 2.2, 2H), 2.24 (m, 1H), 1.50-1.35 (m, 4H); $^{13}$C NMR (125 Hz, $d_6$-DMSO) δ 154.5, 149.1, 145.0, 138.8, 138.7, 137.5, 134.8, 133.0, 122.2, 69.6, 66.6, 58.1, 50.2, 36.0, 29.7, 27.2; Anal. calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.17. Found: C, 66.23; H, 6.99; N, 17.42.

Example 2

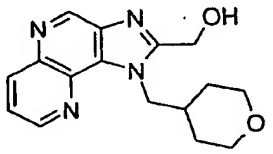
2-(Ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine



2-(Ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine was prepared according to the general methods of Example 1 using ethoxyacetyl chloride in lieu of 3-methoxypropionyl chloride in Part C. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-20% CMA in chloroform) to provide 0.92 g of a brown solid. This material was suspended in cold diethyl ether (10 mL), isolated by filtration, washed with cold diethyl ether, and then dried at 80 °C to provide 0.46 g of 2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as a light grey solid, mp 94-96 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.27 (s, 1H), 9.00 (dd, $J$ = 4.1, 1.6, 1H), 8.52 (dd, $J$ = 8.5, 1.6, 1H), 7.75 (dd, $J$ = 8.5, 4.7, 1H), 4.88 (d, $J$ = 6.3, 2H), 4.85 (s, 2H), 3.78 (dd, $J$ = 11.0, 3.2, 2H), 3.60 (q, $J$ = 6.9, 2H), 3.14 (td, $J$ = 11.3, 2.2, 2H), 2.36 (m, 1H), 1.50-1.35 (m, 4H), 1.16 (t, $J$ = 6.9, 3H); $^{13}$C NMR (125 Hz, $d_6$-DMSO) δ 152.4, 149.2, 145.6, 139.2, 138.4, 137.5, 135.0, 133.6, 122.6, 66.6, 65.6, 64.1, 50.7, 36.0, 29.8, 14.9; Anal. calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.17. Found: C, 65.96; H, 7.00; N, 17.15.

Example 3

[1-(Tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methanol

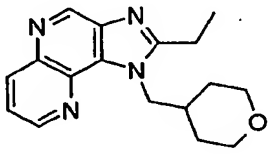


Under a nitrogen atmosphere a solution of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine (1.57 g, 6.08 mmol) in anhydrous dichloromethane (30 mL) was cooled in an ice bath for 10 minutes. Anhydrous triethylamine (1.30 mL, 9.12 mmol) was added in a single portion. Acetoxyacetyl

chloride (0.75 mL, 6.69 mmol) was added dropwise and then the reaction mixture was allowed to stir at ambient temperature until analysis by liquid chromatography (LC) indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure to provide crude 2-oxo-2-({4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino][1,5]naphthyridin-3-yl}amino)ethyl acetate as an orange solid. This material was suspended in anhydrous ethanol (35 mL) and combined with anhydrous triethylamine (3.0 mL, 21.30 mmol). The mixture was placed under a nitrogen atmosphere and heated at 110 °C over the weekend. 50% Sodium hydroxide (1 mL) was added and the reaction mixture was stirred at 100 °C for 1 hour. The reaction mixture was concentrated under reduced pressure and then diluted with chloroform (100 mL). The organic layer was washed sequentially with water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-25% CMA in chloroform) to provide 1.00 g of an off-white solid. This material was suspended in cold diethyl ether (20 mL), isolated by filtration, washed with cold diethyl ether, and then dried at 80 °C to provide 0.94 g of [1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methanol as a light grey solid, mp 186-188 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.25 (s, 1H), 9.00 (dd, $J$ = 4.1, 1.6, 1H), 8.52 (dd, $J$ = 8.5, 1.6, 1H), 7.75 (dd, $J$ = 8.5, 4.7, 1H), 5.80 (t, $J$ = 6.0, 1H), 4.90 (d, $J$ = 6.3, 2H), 4.85 (d, $J$ = 6.0, 2H), 3.78 (dd, $J$ = 11.0, 3.2, 2H), 3.14 (td, $J$ = 11.3, 2.2, 2H), 2.36 (m, 1H), 1.49-1.36 (m, 4H); $^{13}$C NMR (125 Hz, $d_6$-DMSO) δ 155.4, 149.2, 145.5, 139.1, 138.4, 137.5, 135.1, 133.6, 66.6, 56.4, 50.6, 36.0, 29.8; Anal. calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.40; H, 5.98; N, 19.11.

Example 4

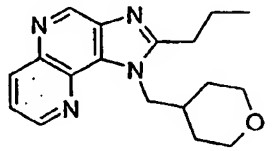
2-Ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine



A mixture of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine (1.25 g, 4.84 mmol), triethyl orthopropionate (1.20 mL, 5.81 mmol), pyridine hydrochloride (25 mg, 0.22 mmol), and toluene (20 mL) was placed in a hot (130 °C) oil bath. After about 4 hours additional pyridine hydrochloride (25 mg) was added and the reaction mixture was heated overnight. Analysis by liquid chromatography/mass spectroscopy (LC/MS) showed that the reaction was incomplete. Additional toluene (50 mL) was added and the reaction flask was equipped with a Dean-Stark trap. After 3 hours analysis by LC/MS indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-25% CMA in chloroform) to provide an off-white solid. This material was suspended in hexanes (20 mL), isolated by filtration, washed with hexanes, and then dried at 80 °C to provide 458 mg of 2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as a light pink solid, mp 132-134 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.23 (s, 1H), 8.98 (dd, $J$ = 4.1, 1.6, 1H), 8.49 (dd, $J$ = 8.5, 1.6, 1H), 7.71 (dd, $J$ = 8.5, 4.7, 1H), 4.80 (d, $J$ = 6.3, 2H), 3.78 (dd, $J$ = 11.0, 3.2, 2H), 3.15 (td, $J$ = 11.3, 2.2, 2H), 3.02 (q, $J$ = 7.5, 2H), 2.36 (m, 1H), 1.49-1.36 (m, 7H); $^{13}$C NMR (125 Hz, $d_6$-DMSO) δ 157.7, 149.0, 144.9, 138.8, 138.7, 137.4, 134.8, 133.2, 122.1, 66.6, 50.1, 35.9, 29.7, 20.0, 11.4; Anal. calcd for $C_{17}H_{20}N_4O$: C, 68.91; H, 6.80; N, 18.90. Found: C, 68.69; H, 7.08; N, 18.81.

Example 5

2-Propyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine

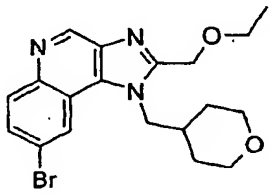


A mixture of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine (1.46 g, 5.65 mmol), trimethyl orthobutyrate (1.2 mL, 6.78 mmol), pyridine hydrochloride (35 mg, 0.28 mmol), and toluene (60 mL) in a flask equipped with a Dean-Stark trap was placed in a hot (150 °C) oil bath. After 1 hour, analysis by LC/MS indicated that starting material had been consumed and that the amide intermediate had formed. Concentrated

hydrochloric acid (3 drops) was added. After 2 hours analysis by LC/MS indicated that the amide had cyclized. The reaction mixture was concentrated under reduced pressure. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-25% CMA in chloroform) to provide 0.97 g of an off-white solid. This material was suspended in cold diethyl ether (20 mL), isolated by filtration, washed with cold diethyl ether, and then dried at 80 °C to provide 0.55 g of 2-propyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as an off-white solid, mp 122-125 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.23 (s, 1H), 8.98 (dd, $J$ = 4.1, 1.6, 1H), 8.49 (dd, $J$ = 8.5, 1.6, 1H), 7.71 (dd, $J$ = 8.5, 4.7, 1H), 4.80 (d, $J$ = 6.3, 2H), 3.78 (dd, $J$ = 11.0, 3.2, 2H), 3.14 (td, $J$ = 11.3, 2.2, 2H), 2.97 (q, $J$ = 7.6, 2H), 2.24 (m, 1H), 1.93 (sextet, $J$ = 7.6, 2H), 1.49-1.35 (m, 4H), 1.04 (t, $J$ = 7.1, 3H); $^{13}$C NMR (125 Hz, $d_6$-DMSO) δ 156.6, 149.0, 144.9, 138.79, 138.74, 137.4, 134.8, 133.0, 122.1, 66.6, 50.1, 36.0, 29.7, 28.3, 20.3, 13.8; Anal. calcd for $C_{18}H_{22}N_4O$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.52; H, 7.38; N, 17.95.

Example 6

8-Bromo-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline




Part A

Phosphorous oxychloride (10.6 mL, 113.8 mmol) was added dropwise to a mixture of 6-bromo-4-hydroxy-3-nitroquinoline (30.00 g, 81.28 mmol) and DMF (250 mL). After 1.5 hours the reaction mixture was poured into ice water (400 mL) with stirring. A solid was isolated by filtration, washed with water, and dried under high vacuum at ambient temperature overnight to provide crude 6-bromo-4-chloro-3-nitroquinoline (>32 g).

Part B

Under a nitrogen atmosphere THF (75 mL) and triethylamine (14.6 mL, 104.4 mmol) were added sequentially to a mixture of crude 6-bromo-4-chloro-3-nitroquinoline

(15.0 g, 52.2 mmol) and 1-tetrahydro-2*H*-pyran-4-ylmethylamine hydrochloride (8.30 g, 54.8 mmol). The reaction mixture was placed in an oil bath at 45 °C for 2 hours and then concentrated under reduced pressure. The residue was diluted with THF (30 mL) and water (200 mL). The THF was removed under reduced pressure. A solid was isolated by filtration and dried to provide 7.55 g of 6-bromo-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine.

Part C

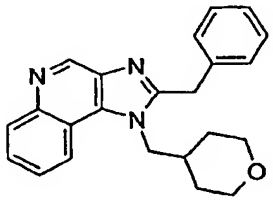
A mixture of 6-bromo-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine (7.56 g), 5% platinum on carbon (0.76 g), methanol (25 mL), and acetonitrile (95 mL) was placed under hydrogen pressure on a Parr apparatus. When the reaction was complete, the mixture was filtered through a layer of CELITE filter agent. The filter cake was washed with acetonitrile. The filtrate was concentrated under reduced pressure to provide 6.94 g of 6-bromo-$N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine as a yellowish-orange oil.

Part D

6-Bromo-$N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (6.94 g, 20.64 mmol) was reacted with ethoxyacetyl chloride (2.5 mL, 22.70 mmol) and then cyclized according to the general method of Example 1 Part C using 6-bromo-$N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine in lieu of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine and ethoxyacetyl chloride in lieu of 3-methoxypropionyl chloride. The crude product was suspended in diethyl ether (20 mL), isolated by filtration, washed with diethyl ether, and then dried at 80 °C to provide 3.03 g of 8-bromo-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 136-139 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.22 (s, 1H), 8.46 (d, $J$ = 2.2, 1H), 8.10 (d, $J$ = 8.9, 1H), 7.85 (dd, $J$ = 8.9, 2.2, 1H), 4.83 (s, 2H), 4.65 (d, $J$ = 7.3, 2H), 3.81 (dd, $J$ = 11.7, 2.5, 2H), 3.60 (q, $J$ = 7.0, 2H), 3.15 (td, $J$ = 11.6, 2.2, 2H), 2.16 (m, 1H), 1.54-1.42 (m, 4H), 1.16 (t, $J$ = 6.9, 3H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 152.3, 145.4, 142.8, 136.5, 132.6, 132.4, 130.0, 123.3, 119.6, 118.8, 66.5, 65.6, 64.2, 50.4, 35.6, 29.9, 14.9; Anal. calcd for $C_{19}H_{22}N_3O_2Br$: C, 56.40; H, 5.49; N, 10.39. Found: C, 56.30; H, 5.45; N, 10.26.

Example 7

2-Benzyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



Part A

Under a nitrogen atmosphere THF (90 mL) and triethylamine (17.5 mL, 125.6 mmol) were added sequentially to a mixture of crude 4-chloro-3-nitroquinoline (13.10 g, 62.81 mmol) and 1-tetrahydro-2*H*-pyran-4-ylmethylamine hydrochloride (10.0 g, 65.95 mmol). The reaction mixture was placed in an oil bath at 45 °C for 1 hour and then concentrated under reduced pressure. The residue was diluted with THF (30 mL) and water (200 mL). The THF was removed under reduced pressure. A solid was isolated by filtration and dried to provide 16.10 g of 3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine as a light yellow solid.

Part B

A mixture of 3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine (2.50 g), 10% palladium on carbon (0.25 g), and ethanol (40 mL) was placed under hydrogen pressure on a Parr apparatus. When the reaction was complete, the mixture was filtered through a layer of CELITE filter agent. The filter cake was washed with ethanol. The filtrate was concentrated under reduced pressure to provide 2.23 g of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine as a yellowish-orange oil.

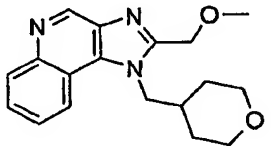
Part C

$N^4$-(Tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (2.23 g, 8.67 mmol) was reacted with phenylacetyl chloride (1.25 mL, 9.54 mmol) and then cyclized according to the general method of Example 1 Part C using $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine in lieu of $N^4$-( tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine and phenylacetyl chloride in lieu of 3-methoxypropionyl chloride. The crude product was suspended in MTBE (20 mL), isolated by filtration, washed sequentially with MTBE and water, and then dried at 80 °C

to provide 459 mg of 2-benzyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 177-180 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.15 (s, 1H), 8.35 (m, 1H), 8.15 (m, 1H), 7.72-7.66 (m, 2H), 7.37-7.23 (m, 5H), 4.54 (d, $J$ = 7.2, 2H), 4.44 (s, 2H), 3.77 (dd, $J$ = 10.6, 2.8, 2H), 3.07 (td, $J$ = 11.6, 1.8, 2H), 2.05 (m, 1H), 1.55-1.38 (m, 4H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 154.5, 144.3, 144.1, 136.8, 136.3, 133.2, 130.3, 128.8, 128.5, 126.6, 126.5, 120.8, 117.5, 66.5, 50.2, 35.7, 33.1, 29.5; Anal. calcd for $C_{23}H_{23}N_3O$: C, 77.28; H, 6.49; N, 11.76. Found: C, 76.89; H, 6.44; N, 11.58.

Example 8

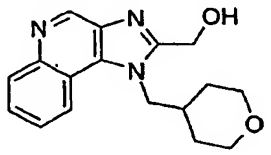
2-(Methoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



$N^4$-(Tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (1.37 g, 5.32 mmol) was reacted with methoxyacetyl chloride (0.55 mL, 5.85 mmol) and then cyclized according to the general method of Example 1 Part C using $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine in lieu of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine and methoxyacetyl chloride in lieu of 3-methoxypropionyl chloride. The crude product was suspended in MTBE (20 mL), isolated by filtration, washed sequentially with MTBE and water, and then dried at 80 °C to provide 101 mg of 2-(methoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 136-139 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.19 (s, 1H), 8.39-8.37 (m, 1H), 8.18-8.16 (m, 1H), 7.75-7.71 (m, 2H), 4.80 (s, 2H), 4.62 (d, $J$ = 7.5, 2H), 3.79 (dd, $J$ = 11.7, 2.5, 2H), 3.37 (s, 3H), 3.13 (td, $J$ = 11.7, 1.9, 2H), 2.18 (m, 1H), 1.52-1.41 (m, 4H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 154.5, 144.3, 144.1, 136.8, 136.3, 133.2, 130.3, 128.8, 128.5, 126.6, 126.5, 120.8, 117.5, 66.5, 50.2, 35.7, 33.1, 29.5; Anal. calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.21; H, 6.77; N, 13.59.

Example 9

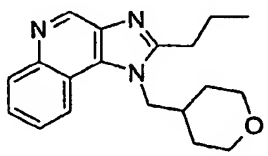
[1-(Tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol



[1-(Tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol was prepared according to the general method of Example 3 using $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine in lieu of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-25% CMA in chloroform) to provide 1.47 g of an off-white solid. This material was suspended in cold diethyl ether (20 mL), isolated by filtration, washed with cold diethyl ether, and then dried at 80 °C to provide 1.07 g of [1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as an off-white solid, mp 165-169 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.16 (s, 1H), 8.39-8.37 (m, 1H), 8.17-8.15 (m, 1H), 7.74-7.70 (m, 2H), 5.77 (t, $J$ = 5.7, 1H), 4.84 (d, $J$ = 6.0, 2H), 4.66 (d, $J$ = 7.2, 2H), 3.79 (dd, $J$ = 5.0, 2.5, 2H), 3.14 (td, $J$ = 12.0, 2.2, 2H), 2.19 (m, 1H), 1.51-1.40 (m, 4H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 154.7, 144.7, 144.2, 136.0, 133.5, 130.3, 126.8, 126.5, 121.0, 117.6, 66.5, 56.6, 50.3, 35.6, 29.7; Anal. calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.32; H, 6.21; N, 13.86.

Example 10

2-Propyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline

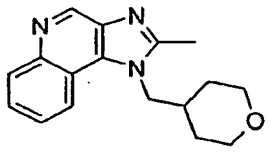


A mixture of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (2.20 g, 8.55 mmol), trimethyl orthobutyrate (1.9 mL, 10.69 mmol), pyridine hydrochloride (50 mg, 0.43 mmol), and toluene (90 mL) in a flask equipped with a Dean-Stark trap was

placed in a hot (150 °C) oil bath. After 3.5 hours, analysis by LC/MS indicated that the reaction was complete. The reaction was concentrated under reduced pressure. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-20% CMA in chloroform) to provide an off-white solid. This material was suspended in cold MTBE (20 mL), isolated by filtration, washed with cold MTBE, and then dried at 80 °C to provide 763 mg of 2-propyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 126-129 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.14 (s, 1H), 8.34-8.33 (m, 1H), 8.15-8.13 (m, 1H), 7.71-7.66 (m, 2H), 4.54 (d, $J$ = 7.2, 2H), 3.79 (dd, $J$ = 10.1, 2.95, 2H), 3.13 (td, $J$ = 11.7, 2.3, 2H), 2.95 (t, $J$ = 7.6, 2H), 2.12 (m, 1H), 1.90 (sextet, $J$ = 7.6, 2H), 1.53-1.45 (m, 4H), 1.04 (t, $J$ = 7.2, 3H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 155.9, 144.2, 144.0, 136.3, 133.0, 130.3, 126.43, 126.40, 120.7, 117.5, 66.5, 49.9, 35.7, 29.6, 28.6, 20.3, 13.8; Anal. calcd for $C_{19}H_{23}N_3O \cdot 1.0\ H_2O$: C, 69.71; H, 7.70; N, 12.84. Found: C, 69.73; H, 7.64; N, 12.85.

Example 11

2-Methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline

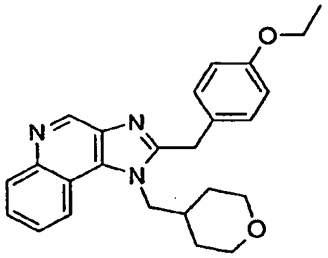


2-Methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general method of Example 10 using triethyl orthoacetate in lieu of trimethyl orthobutyrate. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-20% CMA in chloroform) to provide an off-white solid. This material was recrystallized from boiling MTBE (50 mL), isolated by filtration, washed with cold MTBE, and then dried at 80 °C to provide 763 mg of 2-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 159-162 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.10 (s, 1H), 8.35-8.33 (m, 1H), 8.15-8.13 (m, 1H), 7.72-7.66 (m, 2H), 4.52 (d, $J$ = 7.6, 2H), 3.80 (dd, $J$ = 11.0, 2.5, 2H), 3.16 (td, $J$ = 11.6, 2.5, 2H), 2.66 (s, 3H), 2.15 (m, 1H), 1.53-1.45 (m, 4H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 152.8, 143.99, 143.95, 136.2, 133.0, 130.3, 126.45, 126.42, 120.6, 117.4, 66.5, 50.4, 35.7,

29.7, 14.2; Anal. calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.84; H, 6.96; N, 15.06.

Example 12

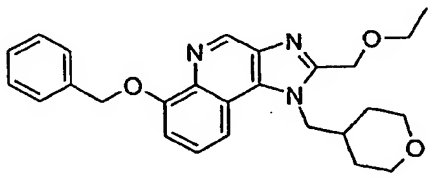
2-(4-Ethoxybenzyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



$N^4$-(Tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (2.75 g, 10.69 mmol) was reacted with 4-ethoxyphenylacetyl chloride (2.1 mL, 11.76 mmol) and then cyclized according to the general method of Example 1 Part C using $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine in lieu of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine and 4-ethoxyphenylacetyl chloride in lieu of 3-methoxypropionyl chloride. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-30% CMA in chloroform) to provide an off-white solid. This material was recrystallized from boiling MTBE (40 mL), isolated by filtration, washed with cold MTBE, and then dried at 80 °C to provide 1.30 g of 2-(4-ethoxybenzyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 162-166 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.15 (s, 1H), 8.36-8.33 (m, 1H), 8.16-8.12 (m, 1H), 7.71-7.66 (m, 2H), 7.25-7.23 (d, $J$ = 8.7, 2H), 6.90-6.85 (d, $J$ = 8.8, 2H), 4.52 (d, $J$ = 7.3, 2H), 4.35 (s, 2H), 3.97 (q, $J$ = 6.9, 2H), 3.77 (dd, $J$ = 11.3, 3.2, 2H), 3.07 (td, $J$ = 11.7, 1.6, 2H), 2.05 (m, 1H), 1.52-1.43 (m, 2H), 1.42-1.32 (m, 2H), 1.29 (t, $J$ = 6.9, 3H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 157.3, 154.8, 144.3, 144.1, 136.3, 133.2, 130.3, 129.8, 128.4, 126.6, 126.4, 120.8, 117.5, 114.4, 66.6, 62.9, 50.2, 35.7, 32.3, 29.5, 14.6; Anal. calcd for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47. Found: C, 74.49; H, 6.65; N, 10.47.

Example 13

6-(Benzyloxy)-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



Part A

Under a nitrogen atmosphere, a mixture of isopropylidene malonate (72 g) and triethyl orthoformate (220 mL) was heated in an oil bath at 100 °C for 3 hours. The reaction mixture was cooled to 60 °C and 2-benzyloxyaniline (114 g) was added in portions. The reaction mixture was allowed to cool to ambient temperature over night and then it was diluted with diethyl ether. A solid was isolated by filtration and washed with diethyl ether to provide 129 g of 5-{[(2-benzyloxy)phenylimino]methyl}-2,2-dimethyl-[1,3]-dioxane-4,6-dione.

Part B

The material from Part A was slowly added to hot (200 °C) DOWTHERM A heat transfer fluid (600 mL). The mixture was heated at 210 °C until refluxing ceased. The reaction mixture was cooled to ambient temperature. A solid was isolated by filtration and washed with diethyl ether to provide 67 g of 8-benzyloxyquinolin-4-ol.

Part C

Nitric acid (3.7 mL, 1.5 eq) was added to a hot (120 °C) solution of 8-benzyloxyquinolin-4-ol (10 g, 1 eq) in propionic acid (100 mL). The reaction mixture was heated at 120 °C for 3 hours and then allowed to cool to ambient temperature. A precipitate was isolated by filtration and washed with water (100 mL) to provide 9.7 g of 8-benzyloxy-3-nitroquinolin-4-ol.

Part D

Phosphorous oxychloride (3.3 mL, 35.72 mmol) was added dropwise to a suspension of 8-benzyloxy-3-nitroquinolin-4-ol (7.56 g, 25.52 mmol) in DMF (250 mL). The reaction mixture was allowed to stir overnight and then it was poured into ice water (150 mL) with stirring. A solid was isolated by filtration, washed with water, and dried

under high vacuum at ambient temperature to provide 8.03 g of 8-benzyloxy-4-chloro-3-nitroquinoline as a yellow solid.

Part E

8-Benzyloxy-4-chloro-3-nitroquinoline (8.03 g, 25.51 mmol) was reacted with 1-tetrahydro-2*H*-pyran-4-ylmethylamine hydrochloride (4.06 mmol, 26.79 mmol) according to the general method of Example 7 Part A using 8-benzyloxy-4-chloro-3-nitroquinoline in lieu of 4-chloro-3-nitroquinoline to provide 7.88 g of 8-benzyloxy-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine as a light brown solid.

Part F

A mixture of 8-benzyloxy-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine (2.00 g), 5% platinum on carbon (0.2 g), methanol (8 mL), and acetonitrile (28 mL) was placed under hydrogen pressure on a Parr apparatus. When the reaction was complete, the mixture was filtered through a layer of CELITE filter agent. The filter cake was washed with acetonitrile. The filtrate was concentrated under reduced pressure to provide 1.85 g of 8-benzyloxy-$N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine as a yellowish-orange oil.

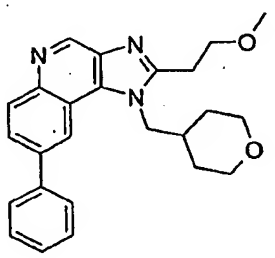
Part G

8-Benzyloxy-$N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (1.85 g, 5.09 mmol) was reacted with ethoxyacetyl chloride (0.60 mL, 5.60 mmol) and then cyclized according to the general method of Example 1 Part C using 8-benzyloxy-$N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine in lieu of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine and ethoxyacetyl chloride in lieu of 3-methoxypropionyl chloride. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-20% CMA in chloroform) to provide 758 mg of 6-(benzyloxy)-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 106-109 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.14 (s, 1H), 7.94 (d, $J$ = 8.8, 1H), 7.62 (t, $J$ = 8.2, 1H), 7.57-7.56 (m, 2H), 7.43-7.40 (m, 2H), 7.36-7.33 (m, 1H), 7.31 (d, $J$ = 7.8, 1H), 5.33 (s, 2H), 4.82 (s, 2H), 4.61 (d, $J$ = 7.3, 2H), 3.80 (dd, $J$ = 12.0, 4.4, 2H), 3.58 (q, $J$ = 6.9, 2H), 3.11 (td, $J$ = 11.7, 1.6, 2H), 2.2 (m, 1H), 1.52-1.43 (m, 2H), 1.42-1.32 (m, 2H), 1.29 (t, $J$ = 6.9, 3H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 155.2, 151.9, 142.9, 137.2, 136.3, 135.9, 133.6, 128.4, 127.8, 127.0, 118.8, 113.0, 108.8, 70.0, 66.6,

65.5, 64.3, 50.5, 35.7, 29.7, 14.9; Anal. calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.12; H, 6.86; N, 9.72.

Example 14

2-(2-Methoxyethyl)-8-phenyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



Part A

6-Bromo-$N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (10.53 g, 31.32 mmol) was reacted with 3-methoxypropionyl chloride (3.7 mL, 34.45 mmol) and then cyclized according to the general method of Example 1 Part C using 6-bromo-$N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine in lieu of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine. The crude product was suspended in diethyl ether (20 mL), isolated by filtration, washed with diethyl ether, and then dried at 80 °C to provide 8.59 g of 8-bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a white solid.

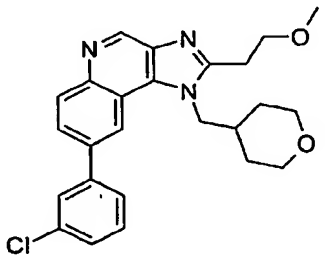
Part B

A mixture of 8-bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.60 g, 1.48 mmol), phenylboronic acid (0.22 g, 1.78 mmol), triphenylphosphine (12 mg, 0.044 mmol), palladium acetate (4 mg, 0.0148 mmol), 1-propanol (10 mL), sodium carbonate (0.19 g, 1.78 mmol), and water (2 mL) was degassed and the backfilled with nitrogen 3 times. The yellow solution was placed in a hot (100 °C) oil bath for about 18 hours. The 1-propanol was removed under reduced pressure. The residue was dissolved in dichloromethane (100 mL), washed with water (50 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a light yellow solid. This material was purified by prep HPLC (silica gel eluted with a

gradient of 0-20% CMA in chloroform) to provide a light yellow solid. This material was recrystallized from boiling 2-propanol (20 mL), isolated by filtration, washed with cold 2-propanol, and dried at 60 °C to provide 375 mg of 2-(2-methoxyethyl)-8-phenyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 204-208 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.15 (s, 1H), 8.44 (d, $J$ = 1.9, 1H), 8.23 (d, $J$ = 8.9, 1H), 8.00 (dd, $J$ = 8.8, 1.9, 1H), 7.84-7.83 (m, 2H), 7.56-7.53 (m, 2H), 7.45-7.42 (m, 1H), 4.66 (d, $J$ = 6.9, 2H), 3.92 (t, $J$ = 6.6, 2H), 3.83 (dd, $J$ = 11.1, 2.5, 2H), 3.30 (s, 3H), 3.26 (t, $J$ = 6.6, 2H), 3.19 (td, $J$ = 11.7, 1.9, 2H), 2.28 (m, 1H), 1.58-1.54 (m, 4H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 153.8, 144.3, 143.3, 140.0, 138.0, 136.6, 133.0, 130.9, 129.1, 127.8, 127.2, 125.7, 118.5, 117.7, 69.7, 66.4, 58.1, 50.1, 35.8, 29.9, 27.4, 25.5; Anal. calcd for $C_{25}H_{27}N_3O_2 \cdot 0.25\ H_2O$: C, 73.94; H, 6.83; N, 10.35. Found: C, 73.98; H, 6.76; N, 10.10.

Example 15

8-(3-Chlorophenyl)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline

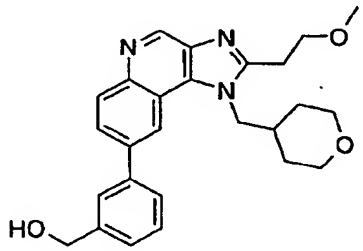


8-Bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.60 g, 1.48 mmol) was coupled with 3-chlorophenylboronic acid (0.28 g, 1.78 mmol) according to the general method of Example 14 Part B. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-20% CMA in chloroform) to provide a light yellow solid. This material was recrystallized from boiling propyl acetate (10 mL), isolated by filtration, washed with cold propyl acetate, and dried at 60 °C to provide 75 mg of 8-(3-chlorophenyl)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 161-164 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.17 (s, 1H), 8.44 (d, $J$ = 1.6, 1H), 8.23 (d, $J$ = 8.9, 1H),

8.02 (dd, $J$ = 8.8, 1.0, 1H), 7.87 (s, 1H), 7.82 (dd, $J$ = 7.6, 0.9, 1H), 7.58 (t, $J$ = 7.9, 1H), 7.50 (d, $J$ = 8.2, 1H), 4.66 (d, $J$ = 5.1, 2H), 3.91 (t, $J$ = 6.6, 2H), 3.85 (d, $J$ = 10.7, 2H), 3.30 (m, 3H), 3.27-3.21 (m, 4H), 2.29 (m, 1H), 1.58-1.51 (m, 4H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 153.9, 144.6, 143.5, 142.1, 136.7, 136.4, 133.9, 133.1, 130.9, 127.6, 127.1, 125.9, 125.5, 119.1, 117.6, 69.7, 66.4, 58.1, 50.0, 35.7, 29.9, 27.4; Anal. calcd for $C_{25}H_{26}N_3O_2Cl$: C, 68.88; H, 6.01; N, 9.64. Found: C, 68.80; H, 5.84; N, 9.41.

Example 16

{3-[2-(2-Methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-8-yl]phenyl}methanol

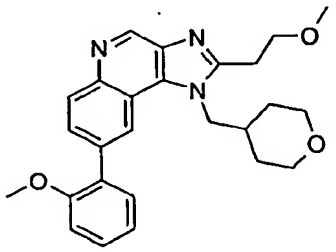



8-Bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.60 g, 1.48 mmol) was coupled with 3-(hydroxymethyl)phenylboronic acid (0.27 g, 1.78 mmol) according to the general method of Example 14 Part B. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 5-30% CMA in chloroform) to provide a light yellow solid. This material was recrystallized from boiling acetonitrile (20 mL), isolated by filtration, washed with cold acetonitrile, and dried at 60 °C to provide 344 mg of {3-[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-8-yl]phenyl}methanol as an off-white solid, mp 171-173 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.15 (s, 1H), 8.42 (d, $J$ = 1.6, 1H), 8.23 (d, $J$ = 8.5, 1H), 8.00 (dd, $J$ = 8.8, 1.9, 1H), 7.77 (s, 1H), 7.70 (dd, $J$ = 7.6, 0.9, 1H), 7.49 (t, $J$ = 7.6, 1H), 7.37 (d, $J$ = 7.6, 1H), 5.26 (t, $J$ = 5.7, 1H), 4.62 (d, $J$ = 6.3, 2H), 4.60 (d, $J$ = 5.7, 2H), 3.91 (t, $J$ = 6.6, 2H), 3.84 (d, $J$ = 11.3, 2H), 3.30 (m, 3H), 3.27-3.19 (m, 4H), 2.29 (m, 1H), 1.56-1.52 (m, 4H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 153.8, 144.3, 143.5, 143.3, 139.7, 138.1, 136.6, 133.0, 130.9, 128.9, 125.9, 125.6, 125.5, 125.2,

118.4, 117.7, 69.7, 66.5, 62.8, 58.1, 50.1, 35.8, 29.8, 27.4; Anal. calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.57; H, 6.61; N, 9.68.

Example 17

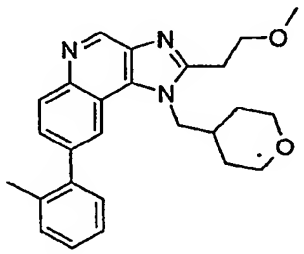
2-(2-Methoxyethyl)-8-(2-methoxyphenyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



8-Bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.60 g, 1.48 mmol) was coupled with 2-methoxyphenylboronic acid (0.27 g, 1.78 mmol) according to the general method of Example 14 Part B. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 5-30% CMA in chloroform) to provide a light yellow solid. This material was recrystallized from boiling hexanes/ethyl acetate (20 mL), isolated by filtration, washed with cold hexanes, and dried at 60 °C to provide 362 mg of 2-(2-methoxyethyl)-8-(2-methoxyphenyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 165-168 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.14 (s, 1H), 8.37 (d, $J$ = 1.9, 1H), 8.15 (d, $J$ = 8.8, 1H), 7.81 (dd, $J$ = 8.6, 1.5, 1H), 7.46 (dd, $J$ = 7.5, 1.6, 1H), 7.47 (td, $J$ = 8.5, 1.6, 1H), 7.20 (d, $J$ = 8.2, 1H), 7.09 (t, $J$ = 7.2, 1H), 4.55 (d, $J$ = 7.3, 2H), 3.91 (t, $J$ = 6.7, 2H), 3.83-3.81 (m, 5H), 3.30 (m, 3H), 3.25-3.19 (m, 4H), 2.29 (m, 1H), 1.56-1.32 (m, 4H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 156.3, 153.6, 144.1, 143.0, 136.4, 136.0, 133.0, 130.8, 129.7, 129.4, 129.3, 128.3, 121.0, 120.9, 117.2, 112.0, 69.7, 66.4, 58.1, 55.8, 50.1, 35.7, 29.7, 27.3; Anal. calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.14; H, 6.63; N, 9.54.

Example 18

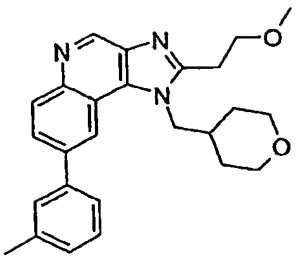
2-(2-Methoxyethyl)-8-(2-methylphenyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



8-Bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.60 g, 1.48 mmol) was coupled with 2-methylphenylboronic acid (0.24 g, 1.78 mmol) according to the general method of Example 14 Part B. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-20% CMA in chloroform) to provide a light yellow solid. This material was recrystallized from boiling hexanes/ethyl acetate (20 mL), isolated by filtration, washed with cold hexanes, and dried at 60 °C to provide 408 mg of 2-(2-methoxyethyl)-8-(2-methylphenyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 180-183 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.17 (s, 1H), 8.17 (d, $J$ = 8.5, 1H), 8.15 (d, $J$ = 1.9, 1H), 7.70 (dd, $J$ = 8.5, 1.6, 1H), 7.38-7.30 (m, 4H), 4.55 (d, $J$ = 7.3, 2H), 3.90 (t, $J$ = 7.0, 2H), 3.81 (dd, $J$ = 11.4, 3.2, 2H), 3.29 (m, 3H), 3.24 (t, $J$ = 6.6, 2H), 3.16 (t, $J$ = 10.4, 2H), 2.35 (s, 3H), 2.21 (m, 1H), 1.47 (qd, $J$ = 12.0, 4.4, 2H), 1.35-1.33 (m, 2H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 153.8, 144.3, 142.9, 141.0, 139.2, 136.6, 134.9, 132.9, 130.5, 129.99, 129.95, 128.1, 127.7, 126.1, 120.7, 117.3, 69.7, 66.4, 58.1, 50.0, 35.6, 29.7, 27.4, 20.2; Anal. calcd for $C_{26}H_{29}N_3O_2$: C, 75.15; H, 7.03; N, 10.11. Found: C, 74.84; H, 6.98; N, 10.08.

Example 19

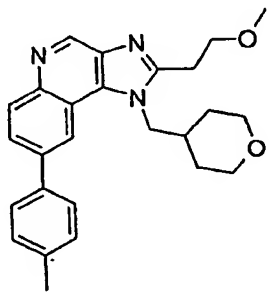
2-(2-Methoxyethyl)-8-(3-methylphenyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



8-Bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.60 g, 1.48 mmol) was coupled with 3-methylphenylboronic acid (0.24 g, 1.78 mmol) according to the general method of Example 14 Part B. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-20% CMA in chloroform) to provide a light yellow solid. This material was recrystallized from boiling hexanes/ethyl acetate (20 mL), isolated by filtration, washed with cold hexanes, and dried at 60 °C to provide 410 mg of 2-(2-methoxyethyl)-8-(3-methylphenyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 138-141 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.14 (s, 1H), 8.41 (d, $J$ = 1.9, 1H), 8.21 (d, $J$ = 8.5, 1H), 7.99 (dd, $J$ = 8.8, 1.9, 1H), 7.63-7.61 (m, 2H), 7.42 (t, $J$ = 7.5, 1H), 7.25 (d, $J$ = 7.2, 1H), 4.62 (d, $J$ = 6.0, 2H), 3.91 (t, $J$ = 7.0, 2H), 3.85 (d, $J$ = 10.7, 2H), 3.30 (m, 3H), 3.27-3.21 (m, 4H), 2.40 (s, 3H), 2.21 (m, 1H), 1.57-1.52 (m, 4H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 153.8, 144.2, 143.3, 139.9, 138.3, 138.1, 136.6, 133.0, 130.8, 129.0, 128.4, 128.0, 125.6, 124.3, 118.5, 117.6, 69.7, 66.4, 58.1, 50.1, 35.7, 29.8, 27.4, 21.1; Anal. calcd for $C_{26}H_{29}N_3O_2$: C, 75.15; H, 7.03; N, 10.11. Found: C, 75.25; H, 6.92; N, 10.00.

Example 20

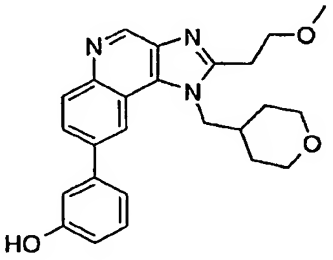
2-(2-Methoxyethyl)-8-(4-methylphenyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



8-Bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.60 g, 1.48 mmol) was coupled with 4-methylphenylboronic acid (0.24 g, 1.78 mmol) according to the general method of Example 14 Part B. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-20% CMA in chloroform) to provide a light yellow solid. This material was recrystallized from boiling hexanes/ethyl acetate (20 mL), isolated by filtration, washed with cold hexanes, and dried at 60 °C to provide 410 mg of 2-(2-methoxyethyl)-8-(3-methylphenyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 150-153 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.13 (s, 1H), 8.40 (d, $J$ = 1.9, 1H), 8.20 (d, $J$ = 8.8, 1H), 7.97 (dd, $J$ = 8.5, 1.9, 1H), 7.72 (d, $J$ = 7.9, 2H), 7.35 (d, $J$ = 7.9, 2H), 4.64 (d, $J$ = 6.4, 2H), 3.91 (t, $J$ = 6.9, 2H), 3.83 (d, $J$ = 12.0, 2H), 3.27 (s, 3H), 3.25 (t, $J$ = 7.0, 2H), 3.19 (t, $J$ = 11.6, 2H), 2.38 (s, 3H), 2.26 (m, 1H), 1.54 (qd, $J$ = 12.9, 4.4, 2H), 1.47 (m, 2H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 153.7, 144.1, 143.2, 137.9, 137.3, 137.1, 136.6, 133.0, 130.8, 129.7, 127.0, 125.5, 118.0, 117.7, 69.7, 66.4, 58.1, 50.1, 35.8, 29.9, 27.4, 20.7; Anal. calcd for $C_{26}H_{29}N_3O_2$: C, 75.15; H, 7.03; N, 10.11. Found: C, 75.02; H, 6.92; N, 10.03.

Example 21

3-[2-(2-Methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-8-yl]phenol

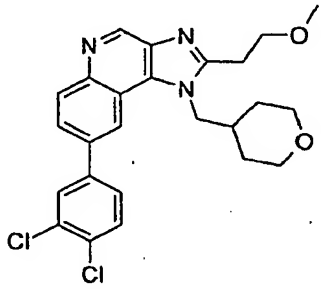



8-Bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.60 g, 1.48 mmol) was coupled with 3-hydroxyphenylboronic acid (0.25 g, 1.78 mmol) according to the general method of Example 14 Part B. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-30%

CMA in chloroform) to provide a light yellow solid. This material was recrystallized from boiling ethanol (20 mL), isolated by filtration, washed with cold ethanol, and dried at 60 °C to provide 150 mg of 3-[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-8-yl]phenol as an off-white solid, mp 256-259 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.61 (s, 1H), 9.14 (s, 1H), 8.38 (d, *J* = 1.6, 1H), 8.20 (d, *J* = 8.5, 1H), 7.92 (dd, *J* = 8.5, 1.9, 1H), 7.32 (t, *J* = 7.8, 1H), 7.23 (d, *J* = 7.9, 1H), 7.18 (t, *J* = 2.2, 1H), 6.83 (dd, *J* = 7.9, 1.5, 1H), 4.62 (d, *J* = 7.0, 2H), 3.91 (t, *J* = 6.6, 2H), 3.83 (d, *J* = 10.8, 2H), 3.30 (m, 3H), 3.25 (t, *J* = 6.7, 2H), 3.20 (t, *J* = 11.3, 2H), 2.25 (m, 1H), 1.54 (qd, *J* = 12.9, 3.5, 2H), 1.53-1.49 (m, 2H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 158.0, 153.8, 144.2, 143.3, 141.4, 138.1, 136.6, 133.0, 130.8, 130.1, 125.6, 118.3, 117.9, 117.6, 114.8, 114.1, 69.7, 66.4, 58.1, 50.1, 35.8, 29.8, 27.4; Anal. calcd for $C_{25}H_{27}N_3O_3 \cdot 0.25\ H_2O$: C, 71.16; H, 6.57; N, 9.96. Found: C, 71.42; H, 6.32; N, 9.90.

Example 22

8-(3,4-Dichlorophenyl)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline

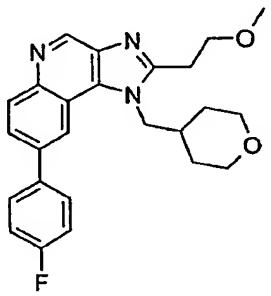


8-Bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.60 g, 1.48 mmol) was coupled with 3,4-dichlorophenylboronic acid (0.25 g, 1.78 mmol) according to the general method of Example 14 Part B. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-20% CMA in chloroform) to provide a light yellow solid. This material was recrystallized from boiling acetonitrile (20 mL), isolated by filtration, washed with cold acetonitrile, and dried at 60 °C to provide 357 mg of 8-(3,4-dichlorophenyl)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 192-195 °C.

$^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.17 (s, 1H), 8.43 (d, $J$ = 1.8, 1H), 8.23 (d, $J$ = 8.8, 1H), 8.08 (d, $J$ = 2.2, 1H), 8.02 (dd, $J$ = 8.5, 1.9, 1H), 7.86 (dd, $J$ = 8.2, 2.2, 1H), 7.80 (d, $J$ = 8.5, 1H), 4.66 (d, $J$ = 5.4, 2H), 3.91 (t, $J$ = 6.6, 2H), 3.83 (d, $J$ = 11.0, 2H), 3.30 (m, 3H), 3.27-3.20 (m, 4H), 2.27 (m, 1H), 1.58-1.50 (m, 4H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 154.0, 144.7, 143.6, 140.6, 136.7, 135.3, 133.0, 131.9, 131.1, 131.0, 130.6, 129.2, 127.3, 125.4, 119.2, 117.5, 69.7, 66.4, 58.1, 50.0, 35.6, 29.9, 27.4; Anal. calcd for $C_{25}H_{25}N_3O_2Cl_2$: C, 63.83; H, 5.36; N, 8.93. Found: C, 63.63; H, 5.07; N, 8.92.

Example 23

8-(4-Fluorophenyl)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline

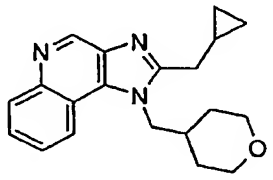


8-Bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.60 g, 1.48 mmol) was coupled with 4-fluorophenylboronic acid (0.25 g, 1.78 mmol) according to the general method of Example 14 Part B. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 0-20% CMA in chloroform) to provide a light yellow solid. This material was recrystallized from boiling hexanes/ethyl acetate (20 mL), isolated by filtration, washed with cold hexanes, and dried at 60 °C to provide 267 mg of 8-(4-fluorophenyl)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 181-184 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.15 (s, 1H), 8.40 (d, $J$ = 1.9, 1H), 8.21 (d, $J$ = 8.9, 1H), 7.98 (dd, $J$ = 8.8, 1.9, 1H), 7.90-7.87 (m, 2H), 7.40-7.36 (m, 2H), 4.65 (d, $J$ = 6.7, 2H), 3.91 (t, $J$ = 6.9, 2H), 3.82 (d, $J$ = 11.3, 1.9, 2H), 3.30 (s, 3H), 3.26 (t, $J$ = 6.7, 2H), 3.18 (td, $J$ = 11.4, 2.2, 2H), 2.24 (m, 1H), 1.56-1.44 (m, 4H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 163.1, 161.1, 153.9, 144.3, 143.2, 136.7 (d, $J$ = 36.4), 136.4 (d, $J$ = 3.9), 133.0, 130.9,

129.23, 129.16, 125.6, 118.4, 117.6, 115.9 (d, $J$ = 22.1), 69.7, 66.4, 58.1, 50.0, 35.7, 29.9, 27.4; Anal. calcd for $C_{25}H_{26}N_3O_2F$: C, 71.58; H, 6.25; N, 10.02. Found: C, 71.51; H, 5.98; N, 9.91.

Example 24

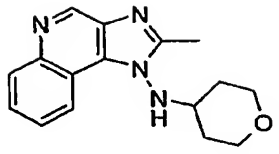
2-(Cyclopropylmethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



$N^4$-(Tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (2.23 g, 8.67 mmol) was reacted with cyclopropylacetyl chloride (1.1 mL, 9.54 mmol) and then cyclized according to the general method of Example 1 Part C using $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine in lieu of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)[1,5]naphthyridine-3,4-diamine and cyclopropylacetyl chloride in lieu of 3-methoxypropionyl chloride. The crude product was suspended in MTBE (20 mL), isolated by filtration, and washed sequentially with MTBE and water. The resulting solid was recrystallized from boiling hexanes/ethyl acetate (20 mL), isolated by filtration, washed with cold hexanes, and dried at 80 °C to provide 572 mg of 2-(cyclopropylmethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 190-193 °C. $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.16 (s, 1H), 8.35-8.33 (m, 1H), 8.15-8.13 (m, 1H), 7.72-7.67 (m, 2H), 4.53 (d, $J$ = 7.3, 2H), 3.79 (dd, $J$ = 11.1, 3.1, 2H), 3.13 (td, $J$ = 11.7, 1.9, 2H), 2.95 (d, $J$ = 6.6, 2H), 2.12 (m, 1H), 1.48 (qd, $J$ = 12.6, 4.1, 2H), 1.43-1.35 (m, 2H), 1.34-1.27 (m, 1H), 0.58-0.54 (m, 2H), 0.32-0.29 (m, 2H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 155.7, 144.3, 144.0, 136.4, 133.0, 130.3, 126.46, 124.40, 120.7, 117.5, 66.5, 50.0, 35.7, 31.4, 29.5, 9.2, 4.7; Anal. calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.51; H, 7.48; N, 13.11.

Example 25

2-Methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine



Part A

Glacial acetic acid (2 mL) was added to a suspension of 2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (2.00 g, 10.1 mmol) in acetonitrile (20 mL) and a solution was obtained. Tetrahydro-4*H*-pyran-4-one (1.86 mL, 20.2 mmol) was added. The reaction mixture was placed under a nitrogen atmosphere and heated to 110 °C. The progress of the reaction was monitored by HPLC. After 3 days the reaction mixture was cooled to ambient temperature, neutralized with 5% sodium carbonate solution (10 mL), and then concentrated under reduced pressure. The residue was partitioned between chloroform (40 mL) and water (10 mL). The organic layer was washed sequentially with water (10 mL) and brine (10 mL), dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 2.82 g of 2-methyl-*N*-(tetrahydro-4*H*-pyran-4-ylidene)-1*H*-imidazo[4,5-*c*]quinolin-1-amine as a tan solid.

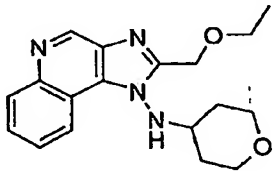
Part B

A solution of the material from Part A (2.82 g, 10.1 mmol) in methanol (40 mL) was chilled in an ice bath. Sodium borohydride (0.764 g, 20.2 mmol) was added in portions over a period of 5 minutes. The reaction mixture was allowed to warm to ambient temperature over a period of 1.5 hours. The reaction mixture was quenched by slowly adding saturated ammonium chloride solution (5 mL) and then concentrated under reduced pressure. The residue was partitioned between chloroform (75 mL) and 10% sodium carbonate solution (20 mL). The organic layer was washed sequentially with water (20 mL) and brine (20 mL), dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide a tan foam. This material was recrystallized twice from acetonitrile to provide 308 mg of 2-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine as tan crystals, mp 209–211 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.07 (s, 1 H), 8.90-8.87 (m, 1 H), 8.12-8.07 (m, 1 H), 7.70-7.65 (m, 2 H), 7.28 (d, $J$ = 2.2 Hz, 1 H), 3.83-3.79 (m, 2 H), 3.52-3.42 (m, 1 H), 3.29-3.20 (m, 2 H), 2.68 (s, 3 H), 1.66-1.42 (m, 4 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 152.5, 143.3, 132.7, 132.5, 129.0, 126.2, 125.2, 120.7, 116.5, 64.5, 55.4, 30.2, 12.6; MS (APCI) *m/z*

283.04 $(M + H)^+$; Anal. Calcd for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.84; Found: C, 67.85; H, 6.44; N, 20.12.

Example 26

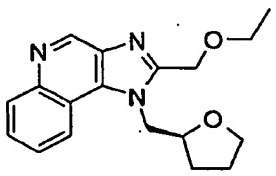
2-(Ethoxymethyl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine



2-(Ethoxymethyl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine was prepared according to the general method of Example 25 using 2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine in lieu of 2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine. The crude product was recrystallized from acetonitrile to provide 415 mg of 2-(ethoxymethyl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine as white crystals, mp 113–116 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.17 (s, 1 H), 8.97-8.94 (m, 1 H), 8.15-8.12 (m, 1 H), 7.73-7.70 (m, 2 H), 7.30 (d, $J$ = 2.2 Hz, 1 H), 4.85 (s, 2 H), 3.85-3.81 (m, 2 H), 3.68-3.59 (m, 1 H), 3.67 (q, $J$ = 7.0 Hz, 2 H), 3.25-3.17 (m, 2 H), 1.68-1.42 (m, 4 H), 1.18 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 152.5, 145.1, 144.6, 133.7, 133.5, 130.1, 127.6, 126.4, 121.9, 117.7, 65.9, 65.6, 63.2, 57.0, 31.1, 15.4; MS (ESI) *m/z* 327.28 $(M + H)^+$; Anal. Calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.16; Found: C, 65.92; H, 6.90; N, 17.19.

Example 27

2-(Ethoxymethyl)-1-[(2*S*)-tetrahydrofuran-2-ylmethyl]-1*H*-imidazo[4,5-*c*]quinoline



Part A

Under a nitrogen atmosphere, triethylamine (2.51 mL, 18.0 mmol) was added to a suspension of 4-chloro-3-nitroquinoline (1.87 g, 8.99 mmol) in dichloromethane (30 mL). The resulting solution was chilled in an ice bath and then (*S*)-(+)-tetrahydrofurfurylamine (1.02 mL, 9.89 mmol) was added. The reaction was allowed to slowly warm to ambient temperature overnight. The reaction mixture was partitioned between chloroform (30 mL) and water (20 mL). The organic layer was washed sequentially with water (20 mL) and brine (20 mL), dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 2.36 g of 3-nitro-*N*-[(2*S*)-tetrahydrofuran-2-ylmethyl]quinolin-4-amine as a yellow/orange solid.

Part B

Platinum on carbon (0.24 g of 5%) was added to a solution of the material from Part A in acetonitrile (100 mL). The mixture was placed under hydrogen pressure (50 psi, 3.4 X $10^5$ Pa) for 4 hours. The reaction mixture was filtered through a layer of CELITE filter agent. The filter cake was rinsed with acetonitrile until the filtrate was clear. The filtrate was concentrated under reduced pressure to provide 2.08 g of $N^4$-[(2*S*)-tetrahydrofuran-2-ylmethyl]quinoline-3,4-diamine as an orange oil.

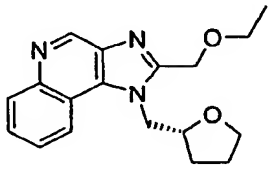
Part C

Triethylamine (2.38 mL, 17.1 mmol) was added to a solution of the material from Part B (2.08 g, 8.55 mmol) in dichloromethane (45 mL). The solution was placed under a nitrogen atmosphere and chilled in an ice water bath. Ethoxyacetyl chloride (1.10 g, 8.98 mmol) was added dropwise over a period of 2 minutes. The reaction mixture was allowed to slowly warm to ambient temperature. After 1.5 hours additional ethoxyacetyl chloride (0.50 mL) was added. The reaction was stirred for 30 minutes and then concentrated under reduced pressure to provide the intermediate amide as an orange oil. The oil was dissolved in ethanol (50 mL). Triethylamine (3.58 mL, 25.7 mmol) and concentrated hydrochloric acid (2 drops) were added and the reaction mixture was heated at 100 °C for 3 hours. The reaction mixture was cooled to ambient temperature and then concentrated under reduced pressure. The residue was dissolved in chloroform (60 mL). The organic solution was washed sequentially with 10% sodium carbonate solution (20 mL), water (20 mL), and brine (20 mL), dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide an orange oil. The oil was purified by prep HPLC (silica gel

eluted with a gradient of 1-20% CMA in chloroform) to provide an orange oil. The oil was triturated with MTBE (about 40 mL) initially at ambient temperature and then in an ice water bath for 1 hour. A solid was isolated by filtration and dried under vacuum at 50 °C overnight to provide 2.10 g of 2-(ethoxymethyl)-1-[(2*S*)-tetrahydrofuran-2-ylmethyl]-1*H*-imidazo[4,5-*c*]quinoline as a white solid, mp 92–94 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.18 (s, 1 H), 8.45-8.43 (m, 1 H), 8.17-8.15 (m, 1 H), 7.73-7.68 (m, 2 H), 4.94-4.90 (m, 2 H), 4.79-4.72 (m, 2 H), 4.33-4.27 (m, 1 H), 3.80-3.76 (m, 1 H), 3.61-3.55 (m, 3 H), 2.18-2.12 (m, 1 H), 1.97-1.90 (m, 1 H), 1.88-1.74 (m, 2 H), 1.17 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 152.3, 145.1, 144.7, 136.2, 134.2, 130.6, 127.3, 126.7, 121.7, 118.1, 77.9, 67.9, 65.9, 64.9, 49.9, 29.0, 25.7, 15.3; MS (APCI) *m/z* 312.18 (M + H)$^+$; Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49; Found: C, 69.39; H, 6.87; N, 13.62.

Example 28

2-(Ethoxymethyl)-1-[(2*R*)-tetrahydrofuran-2-ylmethyl]-1*H*-imidazo[4,5-*c*]quinoline

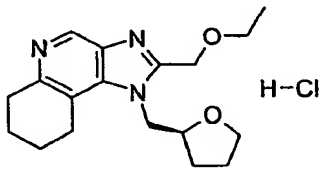


2-(Ethoxymethyl)-1-[(2*R*)-tetrahydrofuran-2-ylmethyl]-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general methods of Example 27 using (*R*)-(-)-tetrahydrofurfurylamine in lieu of (*S*)-(+)-tetrahydrofurfurylamine. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 1-20% CMA in chloroform) to provide an orange oil. The oil was crystallized twice from MTBE to provide 2-(ethoxymethyl)-1-[(2*R*)-tetrahydrofuran-2-ylmethyl]-1*H*-imidazo[4,5-*c*]quinoline as white crystals, mp 89– 92°C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.18 (s, 1 H), 8.46-8.43 (m, 1 H), 8.18-8.15 (m, 1 H), 7.75-7.67 (m, 2 H), 4.95-4.89 (m, 2 H), 4.80-4.70 (m, 2 H), 4.34-4.26 (m, 1 H), 3.82-3.75 (m, 1 H), 3.62-3.55 (m, 3 H), 2.21-2.10 (m, 1 H), 1.98-1.72 (m, 3 H), 1.17 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 152.2, 145.1, 144.7, 136.2, 134.2, 130.6, 127.3, 126.7, 121.7, 118.1, 77.8, 67.9, 65.9, 64.9, 49.9, 29.0, 25.7, 15.3; MS

(APCI) *m/z* 312.19 $(M + H)^+$; Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49; Found: C, 69.31; H, 6.98; N, 13.68.

Example 29

2-(Ethoxymethyl)-1-[(2*S*)-tetrahydrofuran-2-ylmethyl]-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline hydrochloride

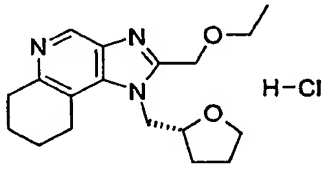



Platinum (IV) oxide (0.430 g, 1.89 mmol) was added to a solution of 2-(ethoxymethyl)-1-[(2*S*)-tetrahydrofuran-2-ylmethyl]-1*H*-imidazo[4,5-*c*]quinoline (0.590 g, 1.89 mmol) in trifluoroacetic acid (25 mL). The mixture was placed under hydrogen pressure (50 psi, 3.4 x $10^5$ Pa) on a Parr apparatus for 24 hours. The reaction mixture was diluted with chloroform (20 mL) and methanol (5 mL) and filtered through a layer of CELITE filter agent. The filter cake was rinsed with additional solvent and the filtrate was concentrated under reduced pressure to provide a clear colorless oil. The oil was suspended in water (15 mL), the pH of the mixture was adjusted to 13 by the dropwise addition of 10% sodium hydroxide, and then it was extracted with dichloromethane (4 x 15 mL). The combined extracts were washed with brine (15 mL), dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide a clear colorless oil. The oil was purified by prep HPLC (silica gel eluted with a gradient of 5-20% CMA in chloroform) to provide a clear colorless oil. The oil was combined with diethyl ether (15 mL) and a solution of hydrochloric acid in ethanol was added dropwise until a precipitate formed. The solid was triturated and chilled in an ice water bath for 30 minutes. The solid was isolated by filtration and dried overnight in a vacuum desiccator to provide 108 mg of 2-(ethoxymethyl)-1-[(2*S*)-tetrahydrofuran-2-ylmethyl]-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline hydrochloride as a white solid, mp 156–159 °C; $^1$H NMR (300 MHz, $D_2O$) δ 8.83 (s, 1 H), 4.98-4.83 (m, 2 H), 4.64 (d, $J$ = 2.4 Hz, 1 H), 4.54-4.45 (m, 1 H), 4.31-4.22 (m, 1 H), 3.89-3.82 (m, 1 H), 3.74-3.62 (m, 3 H), 3.35-3.28 (m, 1 H), 3.13-3.08 (m, 3 H), 2.24-2.14 (m, 1 H), 2.04-1.85 (m, 6 H), 1.78-1.66 (m, 1 H), 1.18 (t,

$J$ = 7.1 Hz, 3 H); $^{13}$C NMR (75 MHz, $D_2O$) δ 159.6, 145.0, 144.8, 137.1, 131.4, 121.9, 79.1, 69.1, 67.7, 64.6, 50.4, 28.9, 27.7, 25.8, 24.2, 21.1, 20.6, 14.4; MS (APCI) *m/z* 316.18 $(M + H)^+$; Anal. Calcd for $C_{18}H_{26}ClN_3O_2 \cdot 0.5H_2O$: C, 59.91; H, 7.54; N, 11.64; Found: C, 59.52; H, 7.57; N, 11.52.

Example 30

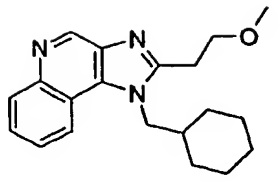
2-(Ethoxymethyl)-1-[(2*R*)-tetrahydrofuran-2-ylmethyl]-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline hydrochloride




2-(Ethoxymethyl)-1-[(2*R*)-tetrahydrofuran-2-ylmethyl]-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline hydrochloride was prepared and purified according to the methods of Example 29 using 2-(ethoxymethyl)-1-[(2*R*)-tetrahydrofuran-2-ylmethyl]-1*H*-imidazo[4,5-*c*]quinoline in lieu of 2-(ethoxymethyl)-1-[(2*S*)-tetrahydrofuran-2-ylmethyl]-1*H*-imidazo[4,5-*c*]quinoline. The product was provided as a white solid, mp 153–155 °C; $^1$H NMR (300 MHz, $D_2O$) δ 8.83 (s, 1 H), 4.90 (q, $J$ = 16.5 Hz, 2 H), 4.64 (d, $J$ = 13.3 Hz, 1 H), 4.49 (dd, $J$ = 15.6, 9.8 Hz, 1 H), 4.31-4.22 (m, 1 H), 3.89-3.81 (m, 1 H), 3.73-3.62 (m, 3 H), 3.35-3.28 (m, 1 H), 3.14-3.07 (m, 3 H), 2.24-2.13 (m, 1 H), 2.02-1.85 (m, 6 H), 1.78-1.67 (m, 1 H), 1.18 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (75 MHz, $D_2O$) δ 159.6, 145.0, 144.8, 137.0, 131.4, 121.9, 79.1, 69.1, 67.7, 64.6, 50.4, 28.9, 27.7, 25.8, 24.2, 21.1, 14.4; MS (APCI) *m/z* 316.19 $(M + H)^+$; Anal. Calcd for $C_{18}H_{26}ClN_3O_2 \cdot 0.7H_2O$: C, 59.32; H, 7.58; N, 11.53; Found: C, 59.17; H, 7.80; N, 11.46.

Example 31

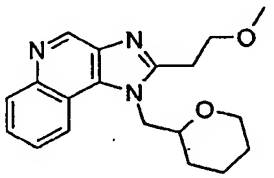
1-Cyclohexylmethyl-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinoline



1-Cyclohexylmethyl-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general methods of Example 27 using cyclohexanemethylamine in lieu of (*S*)-(+)-tetrahydrofurfurylamine in Part A and 3-methoxypropionyl chloride in lieu of ethoxyacetyl chloride in Part C. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 1-12% CMA in chloroform) to provide a yellow solid. The solid was recrystallized twice from acetonitrile and dried in a vacuum oven at 80 °C to provide 1-cyclohexylmethyl-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinoline as white crystals, mp 129–131 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.15 (s, 1 H), 8.32-8.29 (m, 1 H), 8.17-8.14 (m, 1 H), 7.74-7.66 (m, 2 H), 4.49 (d, $J$ = 7.4 Hz, 2 H), 3.90 (t, $J$ = 6.8 Hz, 2 H), 3.31 (s, 3 H), 3.23 (t, $J$ = 6.7 Hz, 2 H), 1.92-1.80 (m, 1 H), 1.67-1.54 (m, 5 H), 1.26-0.99 (m, 5 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 154.0, 144.6, 144.4, 136.6, 133.3, 130.7, 126.9, 126.8, 121.0, 117.9, 70.1, 58.5, 51.0, 38.6, 30.0, 27.8, 26.1, 25.7; MS (ESI) *m/z* 324.23 $(M + H)^+$; Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.27; H, 7.79; N, 12.99; Found: C, 74.08; H, 7.82; N, 12.77.

Example 32

2-(2-Methoxyethyl)-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



Part A

Under a nitrogen atmosphere, sodium azide (2.18 g, 33.5 mmol) was added to a solution of 2-(bromomethyl)tetrahydro-2*H*-pyran (5.00 g, 27.9 mmol) in DMF. The mixture was heated to 50 °C. After 24 hours additional sodium azide (1.5 g) was added.

After a total of 3 days the reaction mixture was cooled to ambient temperature, diluted with diethyl ether (90 mL), and filtered. The organic portion was washed sequentially with water (2 x 30 mL) and brine (30 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 3.88 g of 2-(azidomethyl)tetrahydro-2*H*-pyran as a yellow oil.

Part B

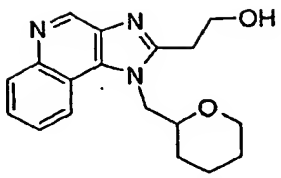
Palladium on carbon (0.39 g of 10%) was added to a solution of the material from Part A in ethanol (30 mL). The mixture was placed under hydrogen pressure (50 psi, 3.4 X $10^5$ Pa) on a Parr apparatus for 15 hours. The reaction mixture was filtered through a layer of CELITE filter agent. The filter cake was rinsed with 1:1 methanol:ethanol. The filtrate was concentrated without heating to provide 2.41 g of 1-tetrahydro-2*H*-pyran-2-ylmethylamine as a clear pale oil.

Part C

2-(2-Methoxyethyl)-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general methods of Example 27 using 1-tetrahydro-2*H*-pyran-2-ylmethylamine in lieu of (*S*)-(+)-tetrahydrofurfurylamine in Part A and 3-methoxypropionyl chloride in lieu of ethoxyacetyl chloride in Part C. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 1-15% CMA in chloroform) to provide a yellow oil. The oil was crystallized and then recrystallized from MTBE/hexanes to provide 2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as white crystals, mp 108–110 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.14 (s, 1 H), 8.35-8.32 (m, 1 H), 8.16-8.13 (m, 1 H), 7.70-7.67 (m, 2 H), 4.75 (dd, *J* = 5.7, 3.0 Hz, 1 H), 4.59 (dd, *J* = 15.8, 9.0 Hz, 1 H), 3.88 (t, *J* = 7.0 Hz, 2 H), 3.77-3.69 (m, 2 H), 3.32 (s, 3 H), 3.28-3.24 (m, 2 H), 3.16-3.08 (m, 1 H), 1.92-1.82 (m, 2 H), 1.50-1.41 (m, 4 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 154.5, 144.5, 136.5, 133.5, 130.6, 126.9, 126.7, 121.2, 117.8, 76.5, 70.0, 68.0, 58.4, 55.3, 50.2, 29.0, 27.8, 25.7, 22.8; MS (APCI) *m/z* 326.20 $(M + H)^+$; Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91; Found: C, 70.31; H, 7.16; N, 13.08.

## Example 33

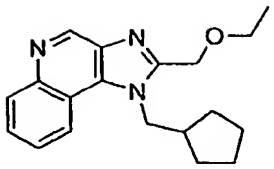
2-[1-(Tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]ethanol



A solution of 2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.54 g, 1.66 mmol) in dichloromethane (17 mL) was placed under a nitrogen atmosphere and chilled in an ice water bath. Boron tribromide (1.74 mL of 1 M in dichloromethane) was added dropwise. The reaction mixture was allowed to slowly warm to ambient temperature overnight. The reaction mixture was concentrated under reduced pressure to provide a tan solid. The solid was combined with a solution of ammonia in methanol (20 mL of 7 N) and stirred for 2 hours. Silica gel (5 g) was added and the mixture was concentrated under reduced pressure to a fine powder. This material was loaded onto a prep HPLC column (100 g of silica gel) and the column was eluted with a gradient of 1-20% CMA in chloroform. The fractions containing product were combined and concentrated under reduced pressure to provide a white foam. The foam was triturated with diethyl ether (10-15 mL) for 2 hours. A solid was isolated by filtration and dried overnight in a vacuum oven to provide 57 mg of 2-[1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]ethanol as an off-white solid, mp 151–153 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.14 (s, 1 H), 8.36-8.33 (m, 1 H), 8.17-8.13 (m, 1 H), 7.71-7.67 (m, 2 H), 4.87 (t, $J$ = 5.4 Hz, 1 H), 4.76 (dd, $J$ = 15.6, 3.0 Hz, 1 H), 4.62(dd, $J$ = 15.7, 6.8 Hz, 1 H), 3.96-3.90 (m, 2 H), 3.78-3.69 (m, 2 H), 3.21-3.09 (m, 3 H), 1.93-1.90 (m, 1 H), 1.84 (br, 1 H), 1.51-1.41 (m, 4 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 155.2, 144.5, 136.5, 133.4, 130.6, 126.9, 126.7, 121.2, 117.9, 76.5, 68.0, 59.6, 50.3, 31.0, 29.1, 25.7, 22.8; MS (APCI) *m/z* 312.20 $(M + H)^+$; Anal. Calcd -or $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49; Found: C, 69.08; H, 6.76; N, 13.28.

Example 34

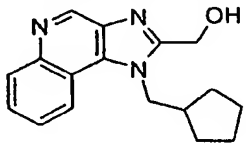
1-Cyclopentylmethyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline



1-Cyclopentylmethyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general methods of Example 27 using cyclopentylmethylamine hydrochloride in lieu of (*S*)-(+)-tetrahydrofurfurylamine in Part A. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 1-15% CMA in chloroform) to provide a tan solid. This material was recrystallized from *n*-propyl acetate to provide 1-cyclopentylmethyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline as amber crystals, mp 95–98 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.19 (s, 1 H), 8.40-8.38 , 1 H), 8.18-8.16 (m, 1 H), 7.75-7.71 (m, 2 H), 4.84 (s, 2 H), 4.68 (d, $J$ = 7.6 Hz, 2 H), 3.59 (q, $J$ = 7.0 Hz, 2 H), 2.55-2.50 (m, 1 H), 1.69-1.56 (m, 4 H), 1.51-1.44 (m, 2 H), 1.43-1.36 (m, 2 H), 1.16 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 151.7, 145.2, 144.7, 136.4, 133.8, 130.7, 127.4, 127.0, 121.5, 118.0, 65.9, 64.8, 50.0, 40.5, 29.8, 24.7, 15.3; MS (ESI) *m/z* 310.32 $(M + H)^+$; Anal. Calcd for $C_{19}H_{23}N_3O$: C, 73.76; H, 7.49; N, 13.58; Found: C, 73.83; H, 7.42; N, 13.61.

Example 35

[1-(Cyclopentylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol

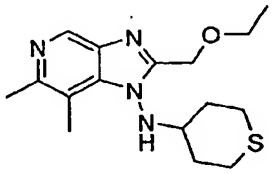


A solution of 1-cyclopentylmethyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline (120 mg, 0.39 mmol) in dichloromethane (20 mL) was placed under a nitrogen atmosphere and chilled in an ice water bath. Boron tribromide (0.58 mL of 1 M in dichloromethane) was added dropwise. The reaction mixture was allowed to slowly warm to ambient temperature overnight. The reaction mixture was quenched with methanol (5 mL) and then concentrated under reduced pressure to provide an orange solid. The solid was combined with a solution of ammonia in methanol (10 mL of 7 N) and stirred for 30

minutes. Silica gel (3 g) was added and the mixture was concentrated under reduced pressure to a fine powder. This material was loaded onto a prep HPLC column (40 g of silica gel) and the column was eluted with a gradient of 1-25% CMA in chloroform. The fractions containing product were combined and concentrated under reduced pressure to provide an off white solid. The solid was recrystallized from acetonitrile and dried in a vacuum oven at 80 °C for 3 hours to provide 46 mg of [1-(cyclopentylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as white crystals, mp 168–170 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.17 (s, 1 H), 8.40-8.38 (m, 1 H), 8.17-8.15 (m, 1 H), 7.74-7.70 (m, 2 H), 5.79 (t, $J$ = 5.8 Hz, 1 H), 4.84 (d, $J$ = 5.9 Hz, 2 H), 4.72 (d, $J$ = 7.7 Hz, 2 H), 2.54-2.49 (m, 1 H), 1.70-1.58 (m, 4 H), 1.52-1.44 (m, 2 H), 1.42-1.35 (m, 2 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 154.4, 144.6, 144.1, 135.9, 133.3, 130.2, 126.7, 126.4, 121.0, 117.6, 56.6, 49.4, 40.1, 29.4, 24.2; MS (APCI) *m/z* 282.11 $(M + H)^+$; Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93; Found: C, 72.60; H, 6.72; N, 15.02.

Example 36

2-(Ethoxymethyl)-6,7-dimethyl-*N*-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-1-amine



Part A

A mixture of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (40 g, 1 eq), triethylamine (50.4 mL, 2.0 eq), *tert*-butyl carbazate (47.8 g, 2.0 eq), and anhydrous DMF (400 mL) was heated at 65 °C under a nitrogen atmosphere for 2 days. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between 10% sodium carbonate (500 mL) and dichloromethane (500 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (500 mL). The combined organics were concentrated under reduced pressure to provide a dark brown solid: The solid was purified by prep HPLC (silica gel eluted with a gradient of 40-60% ethyl acetate in hexanes) to provide an amber oil. The oil was stirred with toluene and then concentrated

under reduced pressure to provide 43.5 g of *tert*-butyl 2-(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)hydrazinecarboxylate as tan crystals.

Part B

A mixture of *tert*-butyl 2-(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)hydrazinecarboxylate (39.1 g), 5% platinum on carbon (4.0 g), and toluene (800 mL) was placed under hydrogen pressure (50 psi, 3.4 X $10^5$ Pa) on a Parr apparatus for 16 hours. The reaction mixture was filtered through a layer of CELITE filter agent. The filter cake was washed with methanol and dichloromethane. The filtrate was concentrated under reduced pressure to provide 32.8 g of *tert*-butyl 2-(3-amino-2-chloro-5,6-dimethylpyridin-4-yl)hydrazinecarboxylate as a tan solid.

Part C

A mixture of *tert*-butyl 2-(3-amino-2-chloro-5,6-dimethylpyridin-4-yl)hydrazinecarboxylate (24.75 g, 86.3 mmol), triethylamine (18.0 mL, 129 mmol), and dichloromethane (500 mL) was chilled in an ice bath. Ethoxyacetyl chloride (11.6 g, 94.9 mmol) was added dropwise. The reaction mixture was kept cool for 1 hour and then allowed to warm to ambient temperature overnight. Additional ethoxyacetyl chloride (0.3 eq) was added and the reaction mixture was stirred for 2 hours. The reaction mixture was washed with water (100 mL). The organic layer was filtered and then concentrated under reduced pressure to provide the amide intermediate. This material was dissolved in ethanol (175 mL) and water (50 mL). Sodium hydroxide (10.4 g, 259 mmol) was added and the reaction mixture was stirred for 2 hours. The pH of the reaction mixture was adjusted to 11 with hydrochloric acid and sodium carbonate. The reaction mixture was diluted with water (300 mL) and then extracted with dichloromethane (3 x 100 mL). The combined organics were filtered and then concentrated under reduced pressure to provide 27.2 g of *tert*-butyl 4-chloro-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-ylcarbamate as an orange solid.

Part D

Under a nitrogen atmosphere, trifluoroacetic acid (50 mL) was added over a period of 5 minutes to a chilled (ice bath) solution of the material from Part C in dichloromethane (200 mL). The reaction mixture was kept cool for 1 hour and then allowed to warm to ambient temperature. The reaction mixture was concentrated under reduced pressure to provide an amber oil. The oil was partitioned between dichloromethane (250 mL) and

water (250 mL). The pH of the aqueous layer was adjusted to about 12 with sodium carbonate and then the aqueous layer was extracted with dichloromethane (3 x 250 mL). The combined organics were concentrated under reduced pressure to provide an amber oil. The oil was triturated with ethyl acetate to provide 5 g of 4-chloro-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-amine as tan crystals. The mother liquor was purified by prep HPLC (silica gel eluted with a gradient of 0-10% methanol in dichloromethane) to provide 10.8 g of 4-chloro-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-amine as an amber oil which slowly solidified.

Part E

Under a nitrogen atmosphere a mixture of 4-chloro-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-amine (5.95 g, 23.4 mmol), tetrahydrothiopyran-4-one (5.43 g, 46.7 mmol), acetonitrile (60 mL), and glacial acetic acid (20 mL) was heated at reflux for 48 hours. The reaction mixture was allowed to cool to ambient temperature and then concentrated under reduced pressure to provide a brown oil. The oil was partitioned between dichloromethane (100 mL) and 10% sodium carbonate (100 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organics were concentrated under reduced pressure to provide a brown oil. The oil was purified by prep HPLC (silica gel eluted with a gradient of 0-7% methanol in dichloromethane) to provide 6.2 g of 4-chloro-2-(ethoxymethyl)-6,7-dimethyl-*N*-(tetrahydro-4*H*-thiopyran-4-ylidene)-1*H*-imidazo[4,5-*c*]pyridin-1-amine as a yellow solid.

Part F

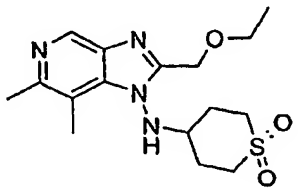
Under a nitrogen atmosphere sodium borohydride (2.0 g, 52.7 mmol) was added over a period of 5 minutes to a solution of the material from Part E (17.6 mmol) in methanol (120 mL). After 2 hours the reaction was quenched with saturated ammonium chloride (40 mL) and then stirred for 5 minutes. The methanol was removed under reduced pressure. The remaining aqueous was combined with sodium carbonate (5 g ) and water (100 mL) and then extracted with dichloromethane (3 x 100 mL). ). The combined organics were concentrated under reduced pressure to provide an amber oil. The oil was purified by prep HPLC (silica gel eluted with a gradient of 0-6% methanol in dichloromethane) to provide 4.96 g of 4-chloro-2-(ethoxymethyl)-6,7-dimethyl-*N*-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-1-amine as a light yellow solid.

Part G

A mixture of 4-chloro-2-(ethoxymethyl)-6,7-dimethyl-*N*-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-1-amine (0.5 g, 1.41 mmol), ammonium formate (0.9 g, 14.8 mol), ethanol (50 mL), and methanol (25 mL) was flushed with nitrogen. 10% Palladium on carbon (0.5 g) was added and the reaction mixture was heated to 80 °C. After 3 hours the reaction mixture was cooled to ambient temperature, additional ammonium formate (0.9 g) and 10% palladium on carbon (0.5 g) were added, and then the reaction mixture was heated at reflux for an additional 3 hours. The reaction mixture was cooled to ambient temperature and then filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure to provide a clear oil. The oil was partitioned between 5% sodium hydroxide (100 mL) and dichloromethane (100 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organics were dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 0.45 g of a clear oil. This material was purified by prep HPLC (silica gel eluted with a gradient of 0-7% methanol in dichloromethane) to provide a clear oil (0.34 g). The oil was crystallized and then recrystallized from ethyl acetate and then dried under high vacuum at 50 °C for 16 hours to provide 0.16 g of 2-(ethoxymethyl)-6,7-dimethyl-*N*-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-1-amine as white crystals, mp 109-111 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.57 (s, 1H), 6.71 (d, $J$ = 1.6 Hz, 1H), 4.71 (s, 2H), 3.61 (q, $J$ = 7.0 Hz, 2H), 3.14 (m, 1H), 2.61 (s, 3H), 2.61-2.53 (m, 4H), 2.50 (s, 3H), 1.84 (m, 2H), 1.49 (m, 2H), 1.15 (t, $J$ = 7.0 Hz, 3H); MS (ESI) *m/z* 321 $(M + H)^+$; Anal. Calcd for $C_{16}H_{24}N_4OS \cdot 0.50\ H_2O$: C, 58.33; H, 7.65; N, 17.01. Found: C, 58.18; H, 7.63; N, 16.91.

Example 37

*N*-(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-amine



Part A

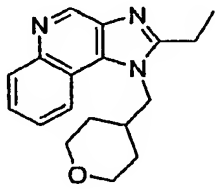
Under a nitrogen atmosphere a mixture of 4-chloro-2-(ethoxymethyl)-6,7-dimethyl-*N*-(tetrahydro-2*H*-thiopyran-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-1-amine (1.00 g, 2.82 mol) and dichloromethane (20 mL) was cooled in an ice bath. 3-Chloroperbenzoic acid (1.78 g of 60%, 6.20 mmol) was added and the reaction mixture was allowed to warm to ambient temperature. Analysis by HPLC indicated that the reaction was complete after 1 hour. The reaction was rerun using 3.46 g of starting material. The two reaction mixtures were combined, washed with 5% sodium carbonate, and then concentrated under reduced pressure to provide 4.2 g of crude 4-chloro-*N*-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-amine as a light orange solid.

Part B

A mixture of 4-chloro-*N*-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-amine (0.5 g, 1.28 mmol), ammonium formate (0.85 g, 13.5 mol), ethanol (40 mL), and methanol (20 mL) was flushed with nitrogen. 10% Palladium on carbon (0.5 g) was added and the reaction mixture was heated to 80 °C for 3 hours. The reaction mixture was cooled to ambient temperature and then filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure to provide a white solid. The solid was partitioned between 5% sodium hydroxide (100 mL) and dichloromethane (100 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organics were dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 0.40 g of a white solid. This material was purified by prep HPLC (silica gel eluted with a gradient of 0-10% methanol in dichloromethane) to provide a white solid (0.34 g). The solid was recrystallized from ethyl acetate/methanol and then dried under high vacuum at 80 °C for 16 hours to provide 0.23 g of *N*-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-amine as white crystals, mp 194-196 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.59 (s, 1H), 6.94 (d, $J$ = 1.3 Hz, 1H), 4.72 (s, 2H), 3.62 (q, $J$ = 7.0 Hz, 2H), 3.44 (m, 1H), 3.21-2.95 (m, 4H), 2.62 (s, 3H), 2.51 (s, 3H), 1.96-1.76 (m, 4H), 1.16 (t, $J$ = 7.0 Hz, 3H); MS (ESI) *m/z* 353 $(M + H)^+$; Anal. Calcd for $C_{16}H_{24}N_4O_3S$: C, 54.53; H, 6.86; N, 15.90. Found: C, 54.54; H, 7.05; N, 15.90.

Example 38

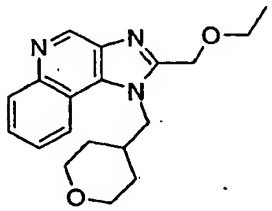
2-Ethyl-1-(tetrahydro-2*H*-pyran-4-yl-methyl)-1*H*-imidazo[4,5-*c*]quinoline



Triethyl orthopropionate (0.938 mL, 4.66 mmol) and pyridine hydrochloride (50 mg, 0.47 mmol) were added sequentially to a solution of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (1.2 g, 4.66 mmol) in toluene (40 mL). The mixture was heated at reflux for 4 hours and then concentrated under reduced pressure. The residue was dissolved in dichloromethane and then washed with water. The organic was dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The resulting solid was dissolved in refluxing acetonitrile. The solution was allowed to cool and then it was concentrated under reduced pressure. The bulk of the residue was again dissolved in refluxing acetonitrile (a small amount of solid remained) and the mixture was allowed to cool. A solid was isolated by filtration, washed with acetonitrile, and dried under vacuum for 2 hours to provide 1.05 g of 2-ethyl-1-(tetrahydro-2*H*-pyran-4-yl-methyl)-1*H*-imidazo[4,5-*c*]quinoline as pale green crystals, mp 169-170 °C. MS (ESI) m/z 296.33 (M + H)$^+$; Anal. Calcd for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 72.99; H, 7.21; N, 14.39.

Example 39

2-(Ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline

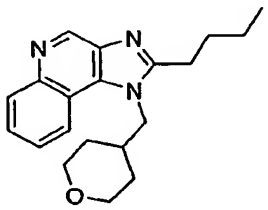


Ethoxyacetyl chloride (0.476 g, 3.89 mmol) was added dropwise to a solution of $N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (1.0 g, 3.89 mmol) in a mixture of dichloromethane (40 mL) and triethylamine (0.540 mL, 3.89mmol). After 30

minutes the dichloromethane was removed under reduced pressure. The crude amide intermediate was dissolved in ethanol (40 mL). Triethylamine (2.6 mL) was added and the reaction mixture was heated to reflux. After 4 hours additional triethylamine (1 mL) was added and the reaction mixture was heated at reflux overnight. Additional triethylamine (1 mL) was added and the reaction mixture was heated at reflux for an additional 2 hours. The reaction mixture was allowed to cool to ambient temperature and then the ethanol was removed under reduced pressure. The residue was dissolved in dichloromethane and then washed with water. The organic was concentrated under reduced pressure. The residue was purified by prep HPLC (silica gel eluted with a linear gradient of 2-15% CMA in chloroform) followed by treatment with refluxing acetonitrile. A solid was isolated by filtration and then dried under vacuum overnight to provide 0.97 g of 2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, m.p. 123.5-125 °C. MS (ESI) m/z 326.24 $(M + H)^+$; Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.25; H, 7.25; N, 13.00.

Example 40

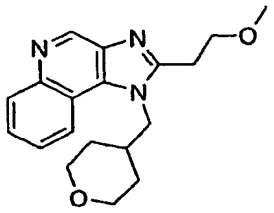
2-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



2-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general method of Example 38 using trimethyl orthovalerate in lieu of triethyl orthopropionate. The crude product was purified by prep HPLC (silica gel eluted with a linear gradient of 2-15% CMA in chloroform) followed by crystallization from acetonitrile to provide 2-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a white solid, m.p. 135-136.5 °C. MS (ESI) m/z 324.05 $(M + H)^+$; Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.27; H, 7.79; N, 12.99. Found: C, 74.25; H, 7.91; N, 13.00

Example 41

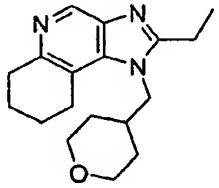
2-(2-Methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline hydrochloride



2-(2-Methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline hydrochloride was prepared according to the general methods of Example 39 using 3-methoxypropionyl chloride in lieu of ethoxyacetyl chloride. The crude product was purified by prep HPLC (silica gel eluted with a linear gradient of 2-15% CMA in chloroform) followed by treatment with refluxing acetonitrile. The resulting oil was diluted with diethyl ether and then combined with a solution of hydrogen chloride in diethyl ether (1.0 mL of 1.0 M). The resulting solid was isolated by filtration, washed with diethyl ether, and dried to provide 0.550 g of 2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline hydrochloride as an off-white solid, m.p. 217 °C, decomposition. MS (ESI) m/z 326.19 $(M + H)^+$; Anal. Calcd for $C_{19}H_{23}N_3O_2 \cdot 1.0HCl$: C, 63.06; H, 6.68; N, 11.61; Cl, 9.80. Found: C, 62.84; H, 6.57; N, 11.33; Cl, 9.55.

Example 42

2-Ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline dihydrochloride

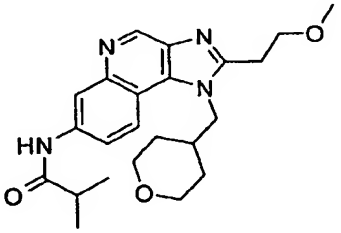


A solution of 2-ethyl-1-(tetrahydro-2*H*-pyran-4-yl-methyl)-1*H*-imidazo[4,5-*c*]quinoline (0.400 g, 1.36 mmol) in trifluoroacetic acid was added to a Parr vessel containing platinum IV oxide (0.300 g, 1.25 mmol) wetted with trifluoroacetic acid. The vessel was placed under hydrogen pressure over the weekend. The reaction mixture was

filtered through a layer of CELITE filter agent. The filter cake was rinsed with 10% methanol in dichloromethane. The filtrate was concentrated under reduced pressure. The residue was made basic with saturated aqueous sodium carbonate and a small amount of 50% sodium hydroxide and then extracted with dichloromethane (2 x 50 mL). The combined organics were washed sequentially with water and brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was purified by prep HPLC (silica gel eluted with a gradient of 5-25% methanol in chloroform) and then dissolved in dichloromethane. The solution was evaporated and the residue was dissolved in diethyl ether (5 mL) and treated with a solution of hydrogen chloride in diethyl ether (3.0 mL of 1.0 M). The resulting precipitate was isolated by filtration. The solid was combined with acetonitrile and heated to reflux. The mixture was allowed to cool with stirring. A solid was isolated by filtration, washed with acetonitrile, and then dried under vacuum to provide 0.224 g of 2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline dihydrochloride as a white powder, m.p. 251-252.5 °C. MS (ESI) m/z 300.21 $(M + H)^+$; Anal. Calcd for $C_{18}H_{25}N_3O \cdot 2.0HCl \cdot 1.0H_2O$: C, 55.39; H, 7.49; N, 10.77; Cl, 18.17. Found: C, 55.42; H, 7.87; N, 10.73; Cl, 18.26.

Example 43

*N*-[2-(2-Methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-2-methylpropanamide

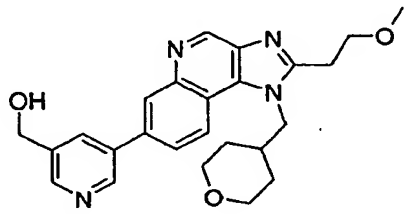


Dioxane (1.3 mL) was added to a mixture of 7-bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.500 g, 1.23 mmol), tris(dibenzylideneacetone)dipalladium (32 mg, 0.031 mmol), cesium carbonate (0.560 g, 1.72 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (54 mg, 0.093 mmol), and isobutyramide (0.127 g, 1.47 mmol) in a vial equipped with a stir bar. The vial was flushed with nitrogen, sealed with a TEFLON lined cap, and then heated at 80 °C

overnight. The reaction mixture was diluted with chloroform containing a trace amount of methanol and then purified by prep HPLC (silica gel eluted with a linear gradient of 2-15% CMA in chloroform). The resulting foamy residue (0.476 g) was dissolved in acetonitrile and then allowed to stand over night. A solid was isolated by filtration, rinsed with acetonitrile, and dried to provide 0.129 g of *N*-[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-2-methylpropanamide as a white solid, m.p. 203-204.5 °C. MS (ESI) m/z 411.28 $(M + H)^+$; Anal. Calcd for $C_{23}H_{30}N_4O_3$: C, 67.29; H, 7.37; N, 13.65. Found: C, 67.28; H, 7.45; N, 13.57.

Example 44

{5-[2-(2-Methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]pyridin-3-yl}methanol

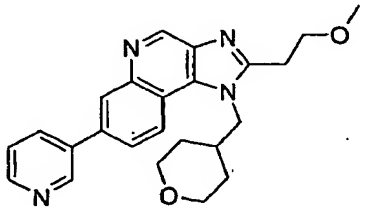



1,2-Dimethoxyethane (5 mL) and water (2.5 mL) were added to a mixture of 7-bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.500 g, 1.24 mmol), 5-(*tert*-butyldimethylsilanyloxymethyl)pyridine-3-boronic acid (0.398 g, 1.49 mmol), and potassium carbonate (0.598 g, 4.34 mmol) and the resulting slurry was sparged with nitrogen. Dichlorobis(triphenylphosphine)palladium(II) (0.043 g, 0.062 mmol) was added. The mixture was sparged with nitrogen and then heated at reflux for 1 hour. The organic layer was purified by prep HPLC (silica gel eluted with a linear gradient of 2-10% CMA in chloroform). The resulting solid was dissolved in a mixture of THF (10 mL) and water (5 mL). Acetic acid (5 mL) was added and the mixture was stirred overnight. The reaction was made basic with 2 M aqueous sodium carbonate and the THF was removed under reduced pressure. A solid was isolated by filtration, washed with water, and dried to provide 0.368 g of {5-[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]pyridin-3-yl}methanol as a white

powder, m.p. 218-220 °C. MS (ESI) m/z 433.20 $(M + H)^+$; Anal. Calcd for $C_{25}H_{28}N_4O_3 \cdot 1.0H_2O$: C, 66.65; H, 6.71; N, 12.43. Found: C, 66.51; H, 6.39; N, 12.34.

Example 45

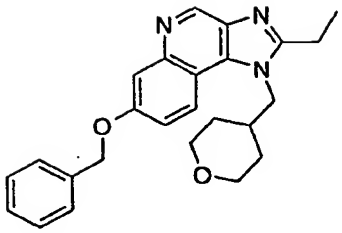
2-(2-Methoxyethyl)-7-pyridin-3-yl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



1,2-Dimethoxyethane (5 mL) and water (2.5 mL) were added to a mixture of 7-bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.500 g, 1.24 mmol), pyridin-3-ylboronic acid (0.183 g, 1.49 mmol), and potassium carbonate (0.598 g, 4.34 mmol) and the resulting slurry was sparged with nitrogen. Dichlorobis(triphenylphosphine)palladium(II) (0.043 g, 0.062 mmol) was added. The mixture was sparged with nitrogen and then heated at reflux for 1 hour. The organic layer was purified by prep HPLC (silica gel eluted with a linear gradient of 2-15% CMA in chloroform). The resulting oil was dissolved in dichloromethane and then the solvent was removed under reduced pressure. This procedure was repeated using acetonitrile to provide 0.474 g of a pale yellow oil. The oil was triturated with diethyl ether and then allowed to stand overnight. A solid was isolated by filtration, washed with diethyl ether, and dried to provide 0.345 g of 2-(2-methoxyethyl)-7-pyridin-3-yl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a white solid, m.p. 150-151 °C. MS (ESI) m/z 403.25 $(M + H)^+$; Anal. Calcd for $C_{24}H_{26}N_4O_2$: C, 71.62; H, 6.51; N, 13.92. Found: C, 71.90; H, 6.85; N, 14.09.

Compound 1

7-Benzyloxy-2-ethyl-1-(tetrahydro-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



Part A

Ammonium hydroxide (1 L) was added to a solution of methyl tetrahydro-2*H*-pyran-4-carboxylate (20 mL, 150 mmol) in methanol (500 mL), and the reaction was stirred overnight at ambient temperature. Additional ammonium hydroxide (500 mL) was added, and the reaction was stirred for four additional days. The methanol was removed under reduced pressure. Solid sodium chloride was added to the aqueous layer, which was extracted with chloroform (3 x 150 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 11.4 g of tetrahydro-2*H*-pyran-4-carboxamide as a white solid.

Part B

A solution of tetrahydro-2*H*-pyran-4-carboxamide (11.4 g, 88.3 mmol) in THF (441 mL) was cooled to 0 °C. Lithium aluminum hydride (10.0 g, 265 mmol) was added in six portions over a period of ten minutes. The reaction flask was purged with nitrogen between the additions. When the reaction mixture was no longer bubbling, it was heated at reflux for six hours. The reaction was then cooled to 0 °C, and ethyl acetate was added dropwise until bubbling ceased. Methanol was then added dropwise until bubbling ceased. Water (10 mL), 15% aqueous sodium hydroxide (10 mL), and water (30 mL) were sequentially added. The organic fraction was decanted off, and the remaining gray solid was washed with chloroform. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide tetrahydro-2*H*-pyran-4-ylmethylamine.

Part C

7-(Benzyloxy)-3-nitroquinolin-4-ol (12.3 g, 41.6 mmol) was slurried in DMF (83 mL). Phosphorous oxychloride (4.2 mL, 45 mmol) was added in one portion and the mixture was heated at 100 °C for 5 minutes. The solution was allowed to cool to 40 °C and was then poured into ice water (total volume 400 mL) resulting in a tan precipitate. The precipitate was filtered and washed with water. After drying, the solid was dissolved

in dichloromethane and the residual water was separated. The organic fraction was dried over anhydrous sodium sulfate and anhydrous magnesium sulfate (about a 50/50 mixture). The organic fraction was filtered into a reaction flask (total volume of organic with 7-(benzyloxy)-3-chloro-4-nitroquinoline is about 425 mL). The flask was cooled to 8 °C and triethylamine (11.6 mL, 83.0mmol) was added. (Tetrahydro-2*H*-pyran-4-yl)methylamine (6.0 g, 52 mmol) in dichloromethane (50 mL) was added dropwise to the mixture. The cooling bath was removed and the reaction was stirred for 16 hours. Water (200 mL) was added followed by stirring for 30 minutes. The layers were separated and the organic fraction was sequentially washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Recrystallization from 2-propanol provided 14.1 g of 7-(benzyloxy)-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine as a yellow powder.

Part D

7-(Benzyloxy)-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine (14.1 g, 35.6 mmol) and 5% platinum on carbon (2.0 g) were added to a Parr vessel. The solids were covered with acetonitrile (200 mL) and placed on a hydrogenator. The vessel was degassed three times, charged with 50 psi ($3.4 \times 10^5$ Pa) hydrogen and allowed to shake for 3 hours, replenishing the hydrogen as needed. After 6 hours, the catalyst was removed by filtration through CELITE filter agent. The CELITE was washed with acetonitrile until the filtrate ran clear (~ 300 mL). The solvent was evaporated to ½ volume under reduced pressure and cooled to 8 °C. Propionyl chloride (3.15 mL, 35.6 mmol) was added dropwise to the solution over 3 minutes. The cooling bath was removed and the reaction was stirred for 16 hours. The resulting precipitate was filtered and washed with acetonitrile. Drying under vacuum for 1 hour provided 14.2 g of *N*-{7-(benzyloxy)-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]quinolin-3-yl}propanamide dihydrochloride as a tan solid.

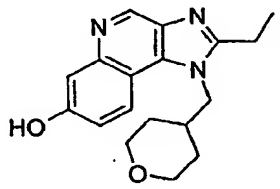
Part E

*N*-{7-(Benzyloxy)-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]quinolin-3-yl}propanamide dihydrochloride (14.2 g, 31.1 mmol) was slurried in ethanol (150 mL) and diluted with water (50 mL). Potassium carbonate (12.3 g, 89 mmol) in water (15 mL) was added and the reaction was stirred until dissolution (~30 minutes). The reaction was then heated to 60 °C for 16 hours. The ethanol was evaporated under reduced pressure and the remaining

water was extracted with dichloromethane. The organic fraction was sequentially washed with water, followed by saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered and concentrated to provide a brown viscous oil. The oil was crystallized from acetonitrile (about 200 mL) to provide 8.4 g of 7-(benzyloxy)-2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a white solid, m.p. 143-145 °C. Anal. Calcd for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47. Found: C, 74.58; H, 7.05; N, 10.50.

Compound 2

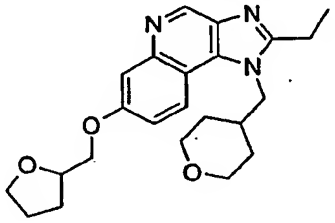
2-Ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-ol




7-(Benzyloxy)-2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (8.3 g, 20.7 mmol) was added to a Parr vessel containing 10% palladium on carbon (1.5 g) wetted with acetonitrile. Methanol (160 mL) was added and the vessel was placed on the hydrogenator. The vessel was degassed three times and charged with 50 psi ($3.4 \times 10^5$ Pa) hydrogen. The vessel was allowed to shake for 16 hours, replenishing the hydrogen as needed. The catalyst was removed by filtration through glass fiber filter paper. The catalyst was washed with 3:1 chloroform/methanol. The filtrates were combined and concentrated under reduced pressure provide 6.1 g of a gray solid. A small portion of this material was purified by prep HPLC (silica gel eluted with a linear gradient of 2-25% CMA in chloroform). The residue was slurried with methanol. The mixture was heated to reflux and then allowed to cool to ambient temperature overnight. A solid was isolated by filtration, washed with methanol, and dried to provide 110 mg of 2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-ol as a white solid, m.p. 318 °C, decomposition. MS (ESI) m/z 312.07 $(M + H)^+$; Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.42; H, 6.89; N, 13.45.

Example 46

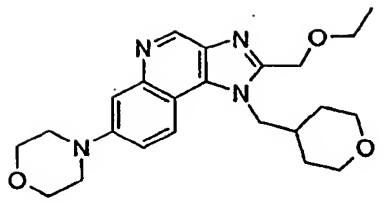
2-Ethyl-7-(tetrahydrofuran-2-ylmethoxy)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



2-Ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-ol (0.800 g, 2.57 mmol), tetrahydrofurfuryl chloride (0.293 mL, 2.70 mmol), cesium carbonate (1.67 g, 5.14 mmol), and DMF (20 mL) were combined and then heated to 65 °C. After 3 hours analysis by LC/MS did not show product. An additional equivalent of the acid chloride was added and the reaction mixture was heated at 100 °C overnight. The reaction mixture was allowed to cool to ambient temperature, diluted with water (80 mL), and then extracted sequentially with ethyl acetate, diethyl ether, and dichloromethane. The ethyl acetate and diethyl ether extracts were combined and then washed with water (2 x 50 mL). The dichloromethane extract was washed with water (3 x 50 mL). The organics were combined, dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was purified twice by prep HPLC (silica gel eluted with a linear gradient of 2-20% CMA in chloroform and then silica gel eluted with a linear gradient of 1-20% CMA in chloroform). The residue was dissolved in a small amount of refluxing ethyl acetate. The solution was diluted with hexanes until it became cloudy and then was allowed to stand. A solid was isolated by filtration and dried to provide 0.214 g of 2-ethyl-7-(tetrahydrofuran-2-ylmethoxy)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a white solid, m.p. 146-147.5 °C. MS (ESI) m/z 396.07 $(M + H)^+$; Anal. Calcd for $C_{23}H_{29}N_3O_3$: C, 69.85; H, 7.39; N, 10.62. Found: C, 69.75; H, 7.43; N, 10.50.

Example 47

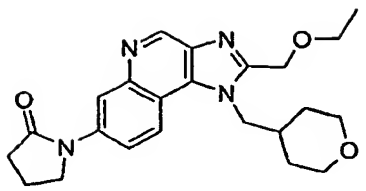
2-Ethoxymethy-7-(morpholin-4-yl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



Under a nitrogen atmosphere, toluene (2.50 mL) was added to a vial containing 7-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.50 g, 1.24 mmol), morpholine (0.11 mL, 1.49 mmol), tris(dibenzylideneacetone)dipalladium (39 mg, 0.037 mmol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (46 mg, 0.074 mmol), and sodium *tert*-butoxide (0.17 g, 1.74 mmol). Nitrogen was bubbled through the mixture. The vial was sealed with a TEFLON lined cap and then heated at 80 °C for 15 hours. The reaction mixture was diluted with chloroform (2 mL) and then filtered through a cotton plug. The filtrate was concentrated under reduced pressure to provide an orange solid. The solid was purified by prep HPLC (silica gel eluted with a gradient of 1-15% CMA in chloroform) to provide a yellow solid. This material was recrystallized from *n*-propyl acetate to provide 150 mg of 2-ethoxymethy-7-(morpholin-4-yl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as white crystals, mp 197–199 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.04 (s, 1 H), 8.22 (d, $J$ = 9.2 Hz, 1 H), 7.53 (d, $J$ = 9.2 Hz, 1 H), 7.47 (d, $J$ = 2.6 Hz, 1 H), 4.79 (s, 2 H), 4.56 (d, $J$ = 7.4 Hz, 2 H), 3.82-3.80 (m, 6 H), 3.58 (q, $J$ = 7.0 Hz, 2 H), 3.31-3.29 (m, 4 H), 3.19-3.10 (m, 2 H), 2.23-2.14 (m, 1 H), 1.52-1.44 (m, 2 H), 1.42-1.35 (m, 2 H), 1.16 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 151.1, 150.2, 146.6, 145.1, 135.1, 134.4, 122.0, 117.9, 112.5, 111.0, 67.0, 66.5, 65.8, 64.7, 50.7, 48.5, 35.9, 30.1, 15.3; MS (APCI) *m/z* 411.10 $(M + H)^+$; Anal. Calcd for $C_{23}H_{30}N_4O_3$: C, 67.29; H, 7.37; N, 13.65; Found: C, 67.18; H, 7.70; N, 14.00.

Example 48

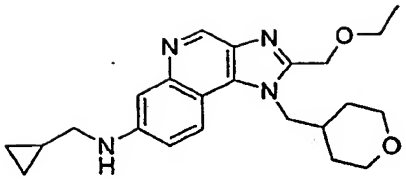
1-[2-Ethoxymethy-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]pyrrolidin-2-one



Under a nitrogen atmosphere, toluene (2.50 mL) was added to a vial containing 7-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.50 g, 1.24 mmol), 2-pyrrolidinone (0.13 mL, 1.49 mmol), tris(dibenzylideneacetone)dipalladium (39 mg, 0.037 mmol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (46 mg, 0.074 mmol), and sodium *tert*-butoxide (0.17 g, 1.74 mmol). Nitrogen was bubbled through the mixture. The vial was capped with a TEFLON lined cap and then heated at 80 °C for 15 hours. The reaction mixture was diluted with chloroform (2 mL) and then filtered through a cotton plug. The filtrate was concentrated under reduced pressure to provide a green solid. The solid was purified by prep HPLC (silica gel eluted with a gradient of 1-15% CMA in chloroform) to provide a yellow solid. This material was recrystallized from *n*-propyl acetate/heptane to provide 0.114 g of 1-[2-ethoxymethy-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]pyrrolidin-2-one as white crystals, mp 145–147 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.16 (s, 1 H), 8.39 (d, $J$ = 9.2 Hz, 1 H), 8.30 (dd, $J$ = 9.2, 2.3 Hz, 1 H), 8.22 (d, $J$ = 2.3 Hz, 1 H), 4.82 (s, 2 H), 4.61 (d, $J$ = 7.4 Hz, 2 H), 4.02 (t, $J$ = 7.0 Hz, 2 H), 3.85-3.75 (m, 2 H), 3.59 (q, $J$ = 7.0 Hz, 2 H), 3.20-3.08 (m, 2 H), 2.59 (t, $J$ = 8.0 Hz, 2 H), 2.29-2.09 (m, 3 H), 1.56-1.35 (m, 4 H), 1.17 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 174.7, 151.8, 145.7, 145.2, 138.8, 135.9, 134.0, 121.8, 119.8, 118.8, 114.2, 67.0, 65.9, 64.7, 48.5, 36.0, 32.8, 30.1, 17.8, 15.3; MS (APCI) *m/z* 409.08 $(M + H)^+$; Anal. Calcd for $C_{23}H_{28}N_4O_3$: C, 67.63; H, 6.91; N, 13.72; Found: C, 67.45; H, 7.10; N, 13.46.

Example 49

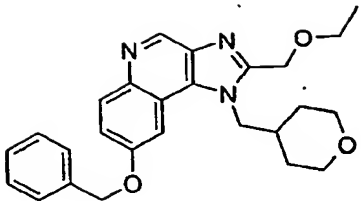
*N*-(Cyclopropylmethyl)-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-amine



Under a nitrogen atmosphere, toluene (2.50 mL) was added to a vial containing 7-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.50 g, 1.24 mmol), cyclopropylmethylamine (0.13 mL, 1.49 mmol), tris(dibenzylideneacetone)dipalladium (39 mg, 0.037 mmol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (46 mg, 0.074 mmol), and sodium *tert*-butoxide (0.17 g, 1.74 mmol). Nitrogen was bubbled through the mixture. The vial was capped with a TEFLON lined cap and then heated at 80 °C for 15 hours. The reaction mixture was diluted with chloroform (2 mL) and then filtered through a cotton plug. The filtrate was concentrated under reduced pressure to provide an orange solid. The solid was purified by prep HPLC (silica gel eluted with a gradient of 1-15% CMA in chloroform) to provide a yellow solid. This material was recrystallized from acetonitrile to provide 0.26 g of *N*-(cyclopropylmethyl)-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-amine as yellow crystals, mp 161–163 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.92 (s, 1 H), 8.05 (d, $J$ = 7.1 Hz, 1 H), 7.16 (dd, $J$ = 9.0, 2.3 Hz, 1 H), 7.05 (d, $J$ = 2.3 Hz, 1 H), 6.22(t, $J$ = 5.4 Hz, 1 H), 4.75 (s, 2 H), 4.50 (d, $J$ = 7.4 Hz, 2 H), 3.85-3.75 (m, 2 H), 3.56 (q, $J$ = 7.0 Hz, 2 H), 3.20-3.07 (m, 2 H), 3.03 (t, $J$ = 6.0 Hz, 2 H), 2.24-2.09 (m, 1 H), 1.53-1.33 (m, 4 H), 1.18-1.08 (m, 4 H), 0.55-0.49 (m, 2 H), 0.30-0.25 (m, 2 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 150.4, 148.5,147.4, 144.5, 134.8, 134.2, 121.7, 117.6, 108.8, 106.8, 67.0, 65.7, 64.7, 50.6, 47.7, 35.9, 30.1, 15.3, 10.8, 4.0; MS (APCI) *m/z* 395.09 $(M + H)^+$; Anal. Calcd for $C_{23}H_{30}N_4O_2$: C, 70.02; H, 7.66; N, 14.20; Found: C, 69.81; H, 7.65; N, 14.17.

Compound 3

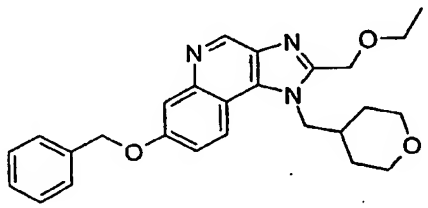
8-(Benzyloxy)-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



8-(Benzyloxy)-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general methods of Example 13 using 4-benzyloxyaniline in lieu of 2-benzyloxyaniline in Part A. The crude product was purified by recrystallization from heptane/ethyl acetate to provide 8-(benzyloxy)-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 105-108 °C. Anal. calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.50; H, 6.60; N, 9.70.

Compound 4

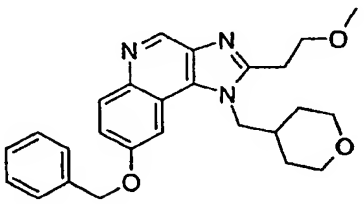
7-(Benzyloxy)-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



7-(Benzyloxy)-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general methods of Example 13 using 3-benzyloxyaniline in lieu of 2-benzyloxyaniline in Part A. The crude product was purified by recrystallization from heptane/ethyl acetate to provide 7-(benzyloxy)-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 136-139 °C. Anal. calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.27; H, 7.05; N, 9.76.

Example 50

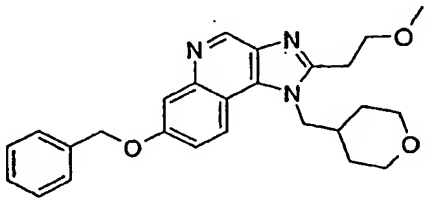
8-(Benzyloxy)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



8-(Benzyloxy)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general methods of Example 13 using 4-benzyloxyaniline in lieu of 2-benzyloxyaniline in Part A and 3-methoxypropionyl chloride in lieu of ethoxyacetyl chloride in Part G. The crude product was purified by recrystallization from heptane/ethyl acetate to provide 8-(benzyloxy)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a beige solid, mp 133-136 °C. Anal. calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.05; H, 6.99; N, 9.60.

Example 51

7-(Benzyloxy)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline

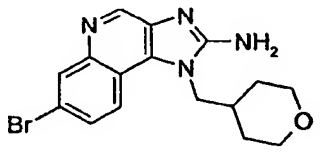


7-(Benzyloxy)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general methods of Example 13 using 3-benzyloxyaniline in lieu of 2-benzyloxyaniline in Part A and 3-methoxypropionyl chloride in lieu of ethoxyacetyl chloride in Part G. The crude product was purified by recrystallization from heptane/ethyl acetate to provide 7-(benzyloxy)-2-(2-methoxyethyl)-

1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a light orange solid, mp 119-122 °C. Anal. calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.26; H, 7.06; N, 9.80.

Example 52

7-Bromo-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-amine




Part A

Triethylamine (43 mL, 0.31 mol) was added in a single portion to a chilled (ice bath) suspension of 7-bromo-4-chloro-3-nitroquinoline (60 g, (0.21 mol) in DMF (200 mL) to provide a solution. A solution of 1-tetrahydro-2*H*-pyran-4-ylmethylamine (36 g, 0.31 mole) in DMF (50 mL) was added dropwise. The reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was chilled in an ice bath, then quenched with water (150 mL), and then stirred for 30 minutes. A solid was isolated by filtration, washed sequentially with water and diethyl ether, and then dried at 65 °C in a vacuum oven to provide 36.2 g of (7-bromo-3-nitroquinolin-4-yl)(tetrahydro-2*H*-pyran-4-ylmethyl)amine as a yellow solid.

Part B

A Parr vessel was charged sequentially with the material from Part A, acetonitrile (1 L), and platinum on carbon (3.7 g). The vessel was placed under hydrogen pressure until analysis by LC/MS indicated that the reaction was complete. Magnesium sulfate was added to the reaction mixture and then it was filtered through a layer of CELITE filter aid. The filtrate was concentrated under reduced pressure to provide 35 g of crude 7-bromo-$N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine as an amber oil.

Part C

A mixture of 7-bromo-$N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (3 g, 9 mmol), cyanogen bromide (1.4 g, 13 mmol), and ethanol (100 mL) was heated at reflux overnight. Analysis by LC/MS indicated that the reaction was incomplete. Two additional equivalents of cyanogen bromide were added. Heating was continued until

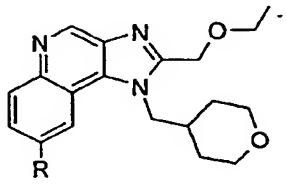
analysis by LC/MS indicated that the reaction was about 80% complete. The reaction mixture was concentrated under reduced pressure to provide a thick brown oil. The oil was dissolved in dichloromethane and washed with water. A precipitate formed in the aqueous layer and was isolated by filtration. This material was converted to the free base by stirring with 2N sodium hydroxide (200 mL) at ambient temperature for 2 hours. The free base was purified by prep HPLC (silica gel eluted with 6.7% methanol in dichloromethane containing 0.4% ammonium hydroxide), washed with diethyl ether, and dried to provide 300 mg of 7-bromo-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-amine as a reddish brown solid, mp >275 °C. Anal. calcd for $C_{16}H_{17}BrN_4O$ • 0.20 HBr: C, 50.95; H, 4.54; N, 14.85. Found: C, 50.58; H, 4.38; N, 14.66.

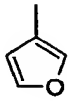
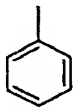
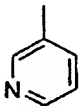
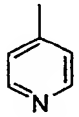
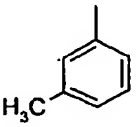
Examples 53 – 92

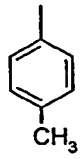
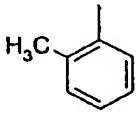
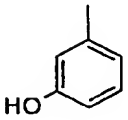
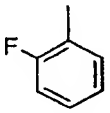
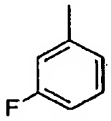
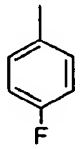
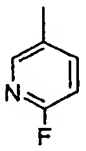
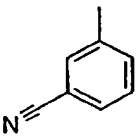
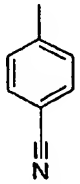
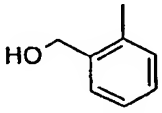
A solution of 8-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (20 mg, 0.10 mmol) in 7:3 volume:volume (v:v) chloroform:methanol (2 mL) was added to a test tube, and the solvent was removed by vacuum centrifugation. The boronic acid (0.11 mmol) indicated in the table below and *n*-propanol (1.6 mL) were sequentially added. The test tube was purged with nitrogen. Palladium (II) acetate (150 µL of a 4 mg/mL solution in toluene, 0.0026 mmol), 2 M aqueous sodium carbonate solution (600 µL), deionized water (113 µL), and a solution of 0.15 mol% triphenylphosphine in *n*-propanol (53 µL, 0.0078 mmol) were sequentially added. The test tube was purged with nitrogen, capped, and then heated at 80 °C overnight in a sand bath. For Example 92, glacial acetic acid (500 µL), tetrahydrofuran (500 µL), and deionized water (500 µL) were added to the test tube. The reaction was heated for 2 hours at 60 °C.

The contents of each test tube were passed through a Waters Oasis Sample Extractions Cartridge MCX (6 cc) according to the following procedure. Hydrochloric acid (3 mL of 1 N) was added to adjust each example to pH <5; and the resulting solution was passed through the cartridge optionally using light nitrogen pressure. The cartridge was washed with methanol (5 mL) optionally using light nitrogen pressure and transferred to a clean test tube. A solution of 1% ammonia in methanol (2 x 5 mL) was then passed through the cartridge optionally using light nitrogen pressure, and the eluent was collected and concentrated by vacuum centrifugation.

The compounds were purified by preparative high performance liquid chromatography using a Waters FractionLynx automated purification system. The fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. The fractions were collected by mass-selective triggering. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



| Example | Reagent | R | Measured Mass (M+H) |
|---|---|---|---|
| 53 | Furan-3-boronic acid |  | 392.1949 |
| 54 | Phenylboronic acid |  | 402.2162 |
| 55 | Pyridine-3-boronic acid |  | 403.2130 |
| 56 | Pyridine-4-boronic acid |  | 403.2136 |
| 57 | 3-Methylphenylboronic acid |  | 416.2337 |

| | | | |
|---|---|---|---|
| 58 | 4-Methylphenylboronic acid |  | 416.2325 |
| 59 | *o*-Tolylboronic acid |  | 416.2321 |
| 60 | 3-Hydroxyphenylboronic acid |  | 418.2174 |
| 61 | 2-Fluorophenylboronic acid |  | 420.2082 |
| 62 | 3-Fluorophenylboronic acid |  | 420.2075 |
| 63 | 4-Fluorophenylboronic acid |  | 420.2081 |
| 64 | 2-Fluoropyridine-5-boronic acid |  | 421.2043 |
| 65 | 3-Cyanophenylboronic acid |  | 427.2116 |
| 66 | 4-Cyanophenylboronic acid |  | 427.2153 |
| 67 | (2-Hydroxymethylphenyl)boronic acid dehydrate |  | 432.2285 |

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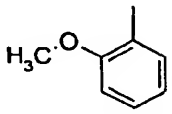
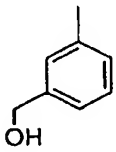
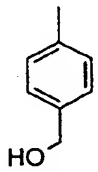
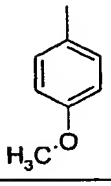
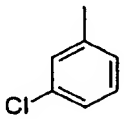
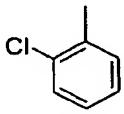
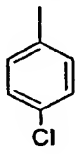
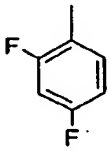
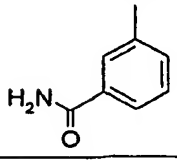
|---|---|---|---|
| 68 | 2-Methoxyphenylboronic acid |  | 432.2315 |
| 69 | 3-(Hydroxymethyl)phenylboronic acid |  | 432.2251 |
| 70 | 4-(Hydroxymethyl)phenylboronic acid |  | 432.2274 |
| 71 | 4-Methoxyphenylboronic acid |  | 432.2293 |
| 72 | 3-Chlorophenylboronic acid |  | 436.1789 |
| 73 | 2-Chlorophenylboronic acid |  | 436.1830 |
| 74 | 4-Chlorophenylboronic acid |  | 436.1783 |
| 75 | 2,4-Difluorophenylboronic acid |  | 438.1984 |
| 76 | (3-Aminocarbonylphenyl)boronic acid |  | 445.2210 |

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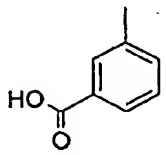
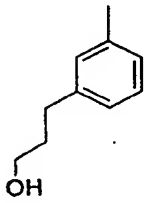
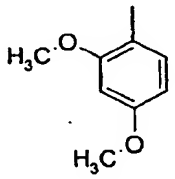
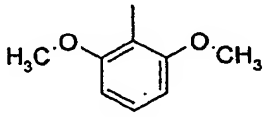
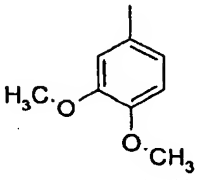
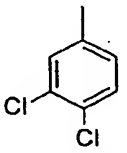
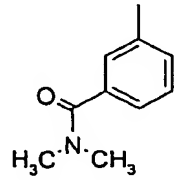
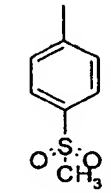
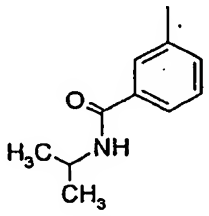
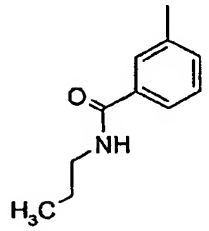
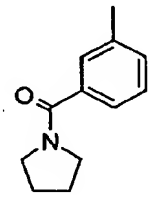
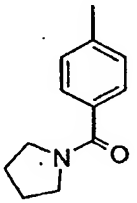
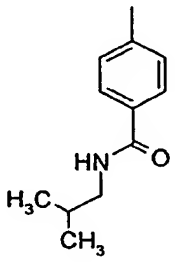
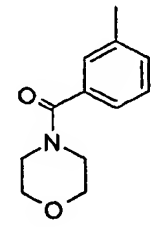
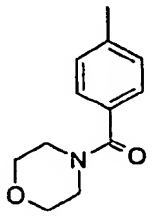
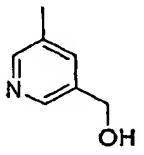
|---|---|---|---|
| 77 | 3-Carboxyphenylboronic acid |  | 446.2083 |
| 78 | [3-(3-Hydroxypropyl)phenyl]boronic acid |  | 460.2553 |
| 79 | 2,4-Dimethoxyphenylboronic acid |  | 462.2361 |
| 80 | 2,6-Dimethoxyphenylboronic acid |  | 462.2346 |
| 81 | 3,4-Dimethoxyphenylboronic acid |  | 462.2392 |
| 82 | 3,4-Dichlorophenylboronic acid |  | 470.1398 |
| 83 | 3-(*N*,*N*-Dimethylaminocarbonyl)phenylboronic acid |  | 473.2522 |
| 84 | 4-(Methanesulfonyl)phenylboronic acid |  | 480.1928 |

| | | | |
|---|---|---|---|
| 85 | 3-(*N*-Isopropylaminocarbonyl)phenylboronic acid |  | 487.2690 |
| 86 | 3-(*N*-Propylaminocarbonyl)phenylboronic acid |  | 487.2708 |
| 87 | 3-(Pyrrolidine-1-carbonyl)phenylboronic acid |  | 499.2691 |
| 88 | 4-(Pyrrolidine –1-carbonyl)phenylboronic acid |  | 499.2702 |
| 89 | 4-(Isobutylaminocarbonyl)phenylboronic acid |  | 501.2860 |
| 90 | 3-(Morpholine-4-carbonyl)phenylboronic acid |  | 515.2625 |

| | | | |
|---|---|---|---|
| 91 | 4-(Morpholine-4-carbonyl)phenylboronic acid |  | 515.2667 |
| 92 | 5-(*tert*-butyldimethylsilanyloxy-methyl)pyridine-3-boronic acid |  | 433.2234 |

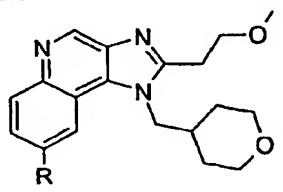
Examples 93 – 128

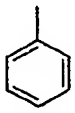
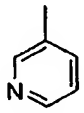
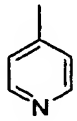
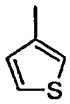
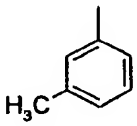
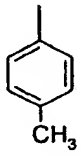
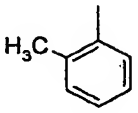
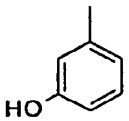
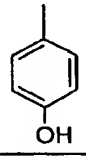
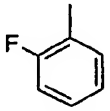
Part A

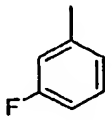
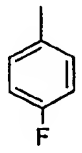
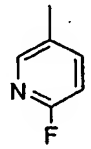
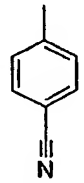
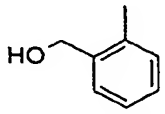
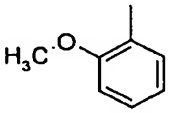
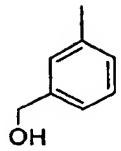
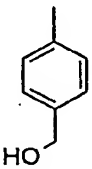
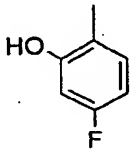
8-Bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general methods of Example 6 using 3-methoxypropionyl chloride in lieu of ethoxyacetyl chloride in Part D. The crude product was triturated with diethyl ether, isolated by filtration, and dried to provide 8-bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a white solid.

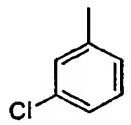
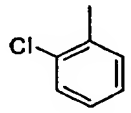
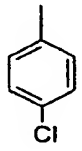
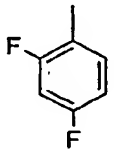
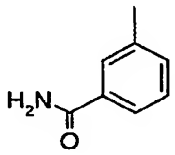
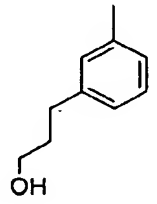
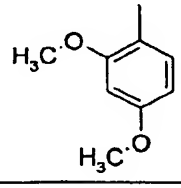
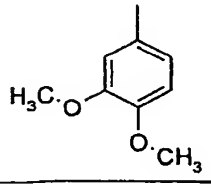
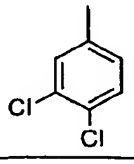
Part B

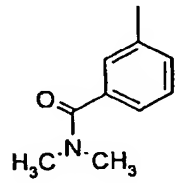
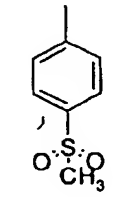
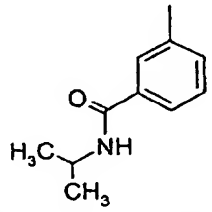
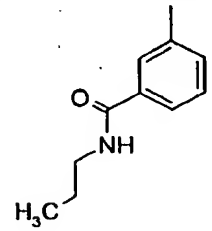
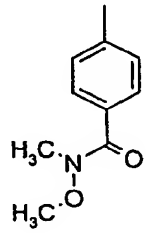
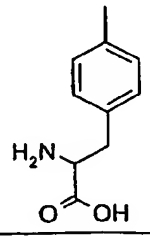
The compounds in the table below were prepared and purified according to the methods of Examples 53 – 92, except that the reactions were heated for 4 hours instead of overnight and 8-bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was used in lieu of 8-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

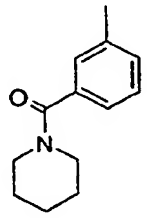
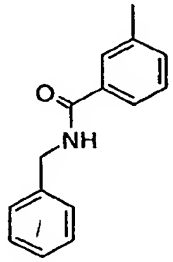
| |
|---|
|  |

| Example | Reagent | R | Measured Mass (M+H) |
|---|---|---|---|
| 93 | Phenylboronic acid |  | 402.2181 |
| 94 | Pyridine-3-boronic acid |  | 403.2119 |
| 95 | Pyridine-4-boronic acid |  | 403.2134 |
| 96 | Thiophene-3-boronic acid |  | 408.1734 |
| 97 | 3-Methylphenylboronic acid |  | 416.2346 |
| 98 | 4-Methylphenylboronic acid |  | 416.2347 |
| 99 | *o*-Tolylboronic acid |  | 416.2316 |
| 100 | 3-Hydroxyphenylboronic acid |  | 418.2113 |
| 101 | 4-Hydroxyphenylboronic acid |  | 418.2138 |
| 102 | 2-Fluorophenylboronic acid |  | 420.2074 |

| | | | |
|---|---|---|---|
| 103 | 3-Fluorophenylboronic acid |  | 420.2082 |
| 104 | 4-Fluorophenylboronic acid |  | 420.2090 |
| 105 | 2-Fluoropyridine-5-boronic acid |  | 421.2070 |
| 106 | 4-Cyanophenylboronic acid |  | 427.2119 |
| 107 | 2-(Hydroxymethyl)phenylboronic acid |  | 432.2302 |
| 108 | 2-Methoxyphenylboronic acid |  | 432.2308 |
| 109 | 3-(Hydroxymethyl)phenylboronic acid |  | 432.2285 |
| 110 | 4-(Hydroxymethyl)phenylboronic acid |  | 432.2278 |
| 111 | 4-Fluoro-2-hydroxyphenylboronic acid |  | 436.2050 |

| | | | |
|---|---|---|---|
| 112 | 3-Chlorophenylboronic acid |  | 436.1798 |
| 113 | 2-Chlorophenylboronic acid |  | 436.1793 |
| 114 | 4-Chlorophenylboronic acid |  | 436.1781 |
| 115 | 2,4-Difluorophenylboronic acid |  | 438.1972 |
| 116 | (3-Aminocarbonylphenyl)boronic acid |  | 445.2233 |
| 117 | [3-(Hydroxypropyl)phenyl]boronic acid |  | 460.2605 |
| 118 | 2,4-Dimethoxyphenylboronic acid |  | 462.2405 |
| 119 | 3,4-Dimethoxyphenylboronic acid |  | 462.2372 |
| 120 | 3,4-Dichlorophenylboronic acid |  | 470.1381 |

| | | | |
|---|---|---|---|
| 121 | 3-(*N,N*-Dimethylaminocarbonyl)phenylboronic acid |  | 473.2595 |
| 122 | 4-(Methanesulfonyl)phenylboronic acid |  | 480.1987 |
| 123 | 3-(*N*-Isopropylaminocarbonyl)phenylboronic acid |  | 487.2720 |
| 124 | 3-(*N*-Propylaminocarbonyl)phenylboronic acid |  | 487.2713 |
| 124 | 4-(*N,O*-Dimethylhydroxylaminocarbonyl)phenylboronic acid |  | 489.2453 |
| 126 | 4-Borono-*DL*-phenylalanine |  | 489.2492 |

| | | | |
|---|---|---|---|
| 127 | 3-(Piperidine-1-carbonyl)phenylboronic acid |  | 513.2829 |
| 128 | 3-(*N*-Benzylaminocarbonyl)phenylboronic acid |  | 535.2704 |

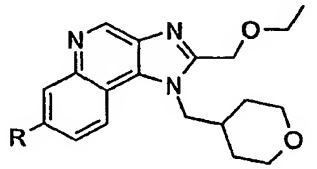
Examples 129 – 157

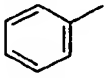
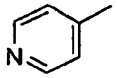
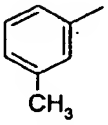
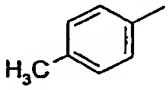
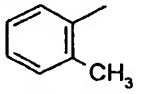
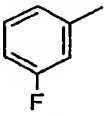
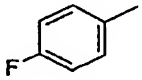
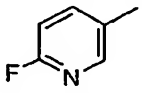
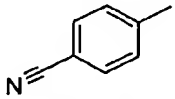
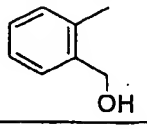
Part A

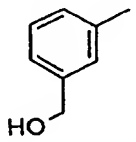
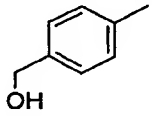
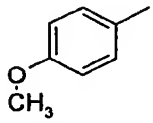
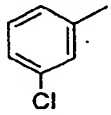
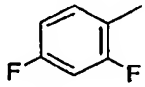
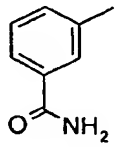
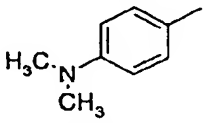
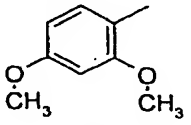
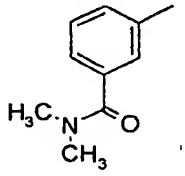
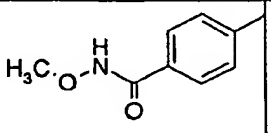
7-Bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general methods of Example 6 using 7-bromo-4-chloro-3-nitroquinoline in lieu of 6-bromo-4-chloro-3-nitroquinoline in Part B. The crude product was triturated with diethyl ether and then recrystallized twice from acetonitrile to provide product as a white crystalline solid.

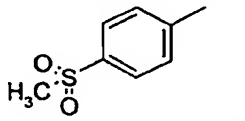
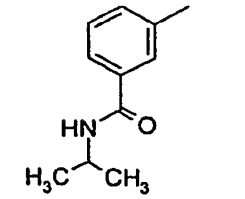
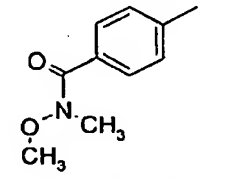
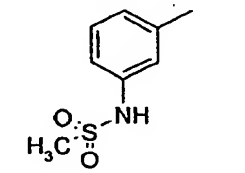
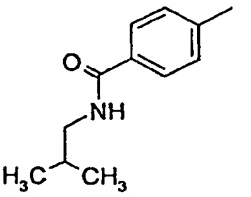
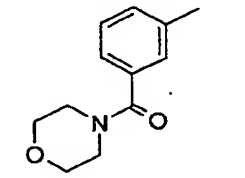
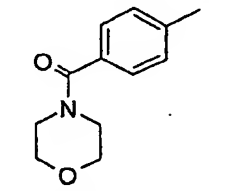
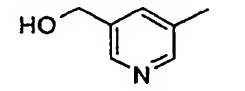
Part B

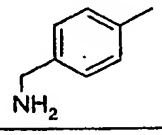
The compounds in the table below were prepared and purified according to the methods of Examples 53 – 92, except that the reactions were heated for 4 hours instead of overnight and 7-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was used in lieu of 8-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline. Example 156 was prepared according to the method used for Example 92, except that it was heated for 4 hours instead of 2 hours. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



| Ex | Reagent | R | Measured Mass (M+H) |
|---|---|---|---|
| 129 | Phenylboronic acid |  | 402.2155 |
| 130 | Pyridine-4-boronic acid |  | 403.2127 |
| 131 | 3-Methylphenylboronic acid |  | 416.2328 |
| 132 | 4-Methylphenylboronic acid |  | 416.2325 |
| 133 | *o*-Tolylboronic acid |  | 416.2361 |
| 134 | 3-Fluorophenylboronic acid |  | 420.2122 |
| 135 | 4-Fluorophenylboronic acid |  | 420.2130 |
| 136 | 2-Fluoropyridine-5-boronic acid |  | 421.2059 |
| 137 | 4-Cyanophenylboronic acid |  | 427.2166 |
| 138 | 2-(Hydroxymethyl)phenylboronic acid |  | 432.2277 |

| | | | |
|---|---|---|---|
| 139 | 3-(Hydroxymethyl)phenylboronic acid |  | 432.2299 |
| 140 | 4-(Hydroxymethyl)phenylboronic acid |  | 432.2272 |
| 141 | 4-Methoxyphenylboronic acid |  | 432.2289 |
| 142 | 3-Chlorophenylboronic acid |  | 436.1785 |
| 143 | 2,4-Difluorophenylboronic acid |  | 438.2017 |
| 144 | (3-Aminocarbonylphenyl)boronic acid |  | 445.2227 |
| 145 | 4-(*N*,*N*-Dimethylamino)phenylboronic acid |  | 445.2577 |
| 146 | 2,4-Dimethoxyphenylboronic acid |  | 462.2397 |
| 147 | 3-(*N*,*N*-Dimethylaminocarbonyl)phenylboronic acid |  | 473.2523 |
| 148 | 4-(Methoxycarbonylamino)phenylboronic acid |  | 475.2379 |

| | | | |
|---|---|---|---|
| 149 | 4-(Methanesulfonyl)phenylboronic acid |  | 480.1941 |
| 150 | 3-(*N*-Isopropylaminocarbonyl)phenylboronic acid |  | 487.2729 |
| 151 | 4-(*N*,*O*-Dimethylhydroxylaminocarbonyl)phenylboronic acid |  | 489.2533 |
| 152 | 3-(Methylsulfonylamino)phenylboronic acid |  | 495.2061 |
| 153 | 4-(Isobutylaminocarbonyl)phenylboronic acid |  | 501.2846 |
| 154 | 3-(Morpholine-4-carbonyl)phenylboronic acid |  | 515.2653 |
| 155 | 4-(Morpholine-4-carbonyl)phenylboronic acid |  | 515.2626 |
| 156 | 5-(*tert*-butyldimethylsilanyloxy-methyl)pyridine-3-boronic acid |  | 433.2259 |

| | | | |
|---|---|---|---|
| 157 | (4-Aminomethylphenyl)boronic acid, pincacol ester, HCl |  | 431.2473 |

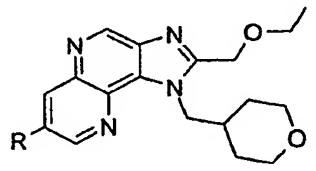
Examples 158 – 204

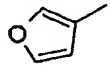
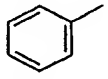
Part A

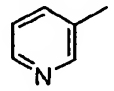
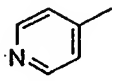
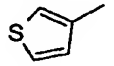
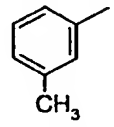
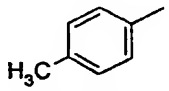
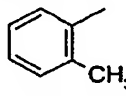
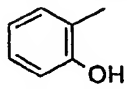
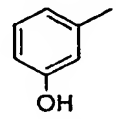
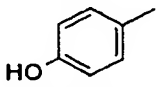
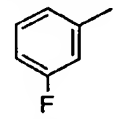
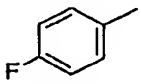
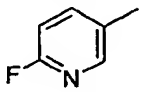
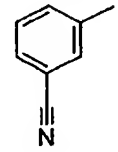
7-Bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine was prepared according to the general methods of Example 6 using 7-bromo-4-hydroxy-3-nitro[1,5]naphthyridine in lieu of 6-bromo-4-hydroxy-3-nitroquinoline in Part A. The crude product was triturated with diethyl ether, isolated by filtration, rinsed with diethyl ether, and dried to provide product as a white solid.

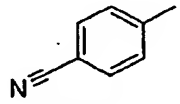
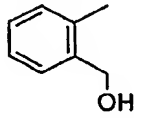
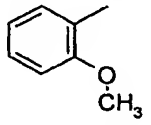
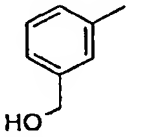
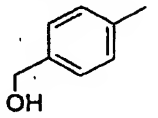
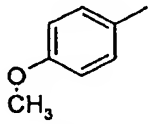
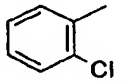
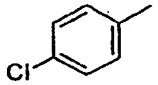
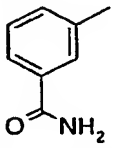
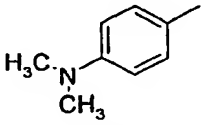
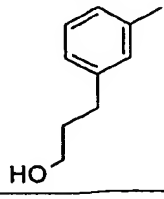
Part B

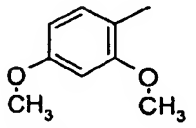
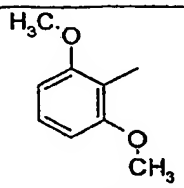
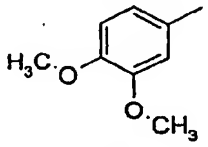
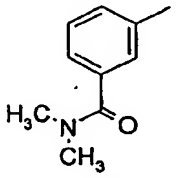
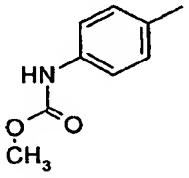
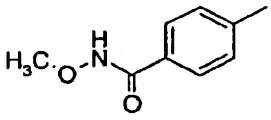
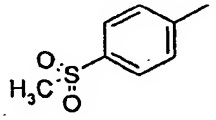
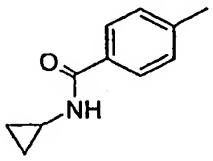
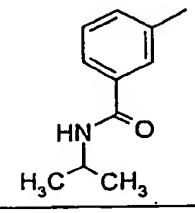
The compounds in the table below were prepared and purified according to the methods of Examples 53 – 92, except that the reactions were heated for 4 hours instead of overnight and 7-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine was used in lieu of 8-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline. Example 204 was prepared according to the method used for Example 92, except that the reaction was heated for 4 hours instead of 2 hours. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

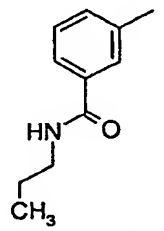
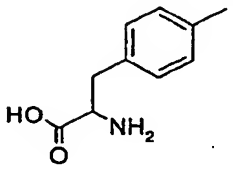
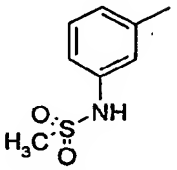
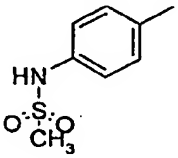
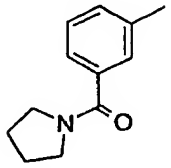
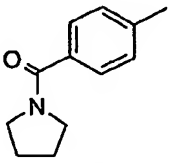
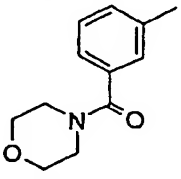
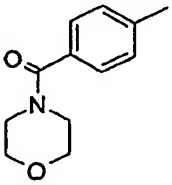


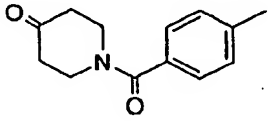
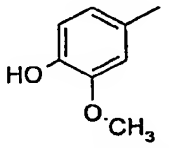
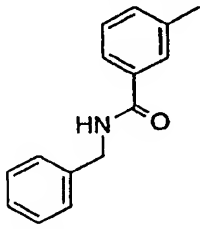
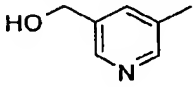
| Ex | Reagent | R | Measured Mass (M+H) |
|---|---|---|---|
| 158 | Furan-3-boronic acid |  | 393.1937 |
| 159 | Phenylboronic acid |  | 403.2137 |

| | | | |
|---|---|---|---|
| 160 | Pyridine-3-boronic acid |  | 404.2075 |
| 161 | Pyridine-4-boronic acid |  | 404.2068 |
| 162 | Thiophene-3-boronic acid |  | 409.1674 |
| 163 | 3-Methylphenylboronic acid |  | 417.2297 |
| 164 | 4-Methylphenylboronic acid |  | 417.2301 |
| 165 | *o*-Tolylboronic acid |  | 417.2288 |
| 166 | 2-Hydroxyphenylboronic acid |  | 419.2082 |
| 167 | 3-Hydroxyphenylboronic acid |  | 419.2094 |
| 168 | 4-Hydroxyphenylboronic acid |  | 419.2086 |
| 169 | 3-Fluorophenylboronic acid |  | 421.2050 |
| 170 | 4-Fluorophenylboronic acid |  | 421.2038 |
| 171 | 2-Fluoropyridine-5-boronic acid |  | 422.1982 |
| 172 | 3-Cyanophenylboronic acid |  | 428.2107 |

| | | | |
|---|---|---|---|
| 173 | 4-Cyanophenylboronic acid |  | 428.2080 |
| 174 | 2-(Hydroxymethyl)phenylboronic acid |  | 433.2243 |
| 175 | 2-Methoxyphenylboronic acid |  | 433.2224 |
| 176 | 3-(Hydroxymethyl)phenylboronic acid |  | 433.2223 |
| 177 | 4-(Hydroxymethyl)phenylboronic acid |  | 433.2221 |
| 178 | 4-Methoxyphenylboronic acid |  | 433.2199 |
| 179 | 2-Chlorophenylboronic acid |  | 437.1726 |
| 180 | 4-Chlorophenylboronic acid |  | 437.1754 |
| 181 | (3-Aminocarbonylphenyl)boronic acid |  | 446.2185 |
| 182 | 4-(*N*,*N*-Dimethylamino)phenylboronic acid |  | 446.2524 |
| 183 | [3-(3-Hydroxypropyl)phenyl]boronic acid |  | 461.2575 |

| | | | |
|---|---|---|---|
| 184 | 2,4-Dimethoxyphenylboronic acid |  | 463.2331 |
| 185 | 2,6-Dimethoxyphenylboronic acid |  | 463.2362 |
| 186 | 3,4-Dimethoxyphenylboronic acid |  | 463.2343 |
| 187 | 3-(*N*,*N*-Dimethylaminocarbonyl)phenylboronic acid |  | 474.2512 |
| 188 | 4-(Methoxycarbonylamino)phenylboronic acid |  | 476.2258 |
| 189 | 4-(*O*-Methylhydroxylaminocarbonyl)phenylboronic acid |  | 476.2281 |
| 190 | 4-(Methanesulfonyl)phenylboronic acid |  | 481.1879 |
| 191 | 4-(Cyclopropylaminocarbonyl)phenylboronic acid |  | 486.2466 |
| 192 | 3-(*N*-Isopropylaminocarbonyl)phenylboronic acid |  | 488.2660 |

| | | | |
|---|---|---|---|
| 193 | 3-(*N*-Propylaminocarbonyl)phenylboronic acid |  | 488.2617 |
| 194 | 4-Borono-*DL*-phenylalanine |  | 490.2462 |
| 195 | 3-(Methylsulfonylamino)phenylboronic acid |  | 496.1994 |
| 196 | 4-(Methylsulfonylamino)phenylboronic acid |  | 496.1989 |
| 197 | 3-(Pyrrolidine-1-carbonyl)phenylboronic acid |  | 500.2642 |
| 198 | 4-(Pyrrolidine-1-carbonyl)phenylboronic acid |  | 500.2633 |
| 199 | 3-(Morpholine-4-carbonyl)phenylboronic acid |  | 516.2590 |
| 200 | 4-(Morpholine-4-carbonyl)phenylboronic acid |  | 516.2601 |

| | | | |
|---|---|---|---|
| 201 | 4-(4-Oxopiperidine-1-carbonyl)phenylboronic acid |  | 528.2632 |
| 202 | 2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol |  | 449.2158 |
| 203 | 3-(*N*-Benzylaminocarbonyl)phenylboronic acid |  | 536.2637 |
| 204 | 5-(*tert*-butyldimethylsilanyloxy-methyl)pyridine-3-boronic acid |  | 434.2174 |

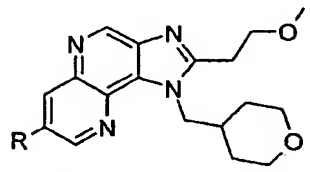
Examples 205 – 240

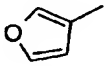
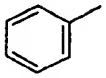
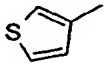
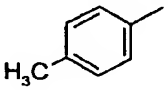
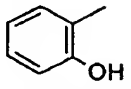
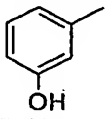
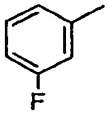
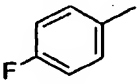
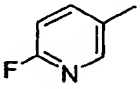
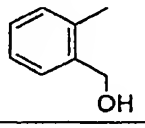
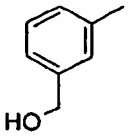
Part A

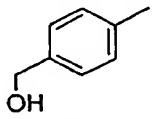
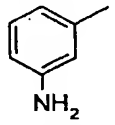
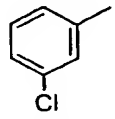
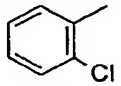
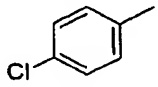
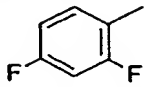
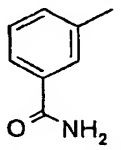
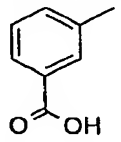
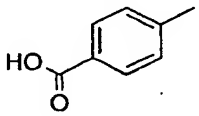
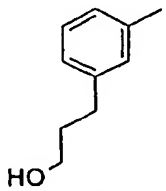
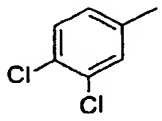
7-Bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine was prepared according to the general methods of Example 6 using 7-bromo-4-hydroxy-3-nitro[1,5]naphthyridine in lieu of 6-bromo-4-hydroxy-3-nitroquinoline in Part A and 3-methoxypropionyl chloride in lieu of ethoxyacetyl chloride in Part D. The crude product was triturated with MTBE, isolated by filtration, rinsed with MTBE, and dried to provide product as a beige solid.

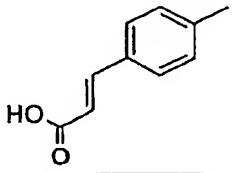
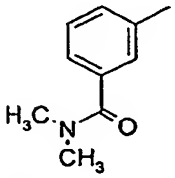
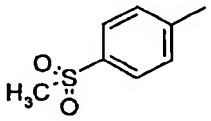
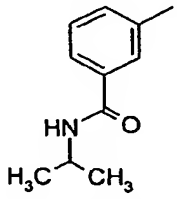
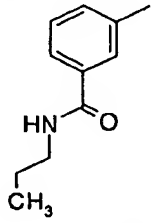
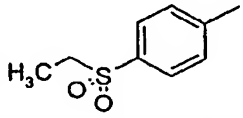
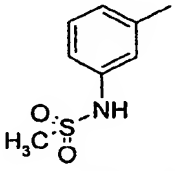
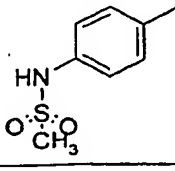
Part B

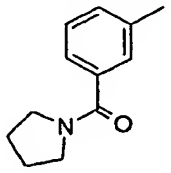
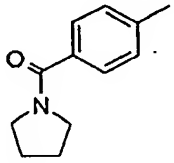
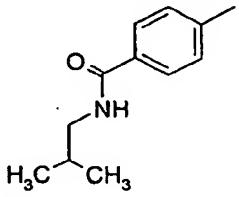
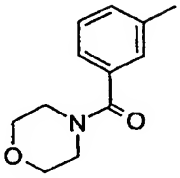
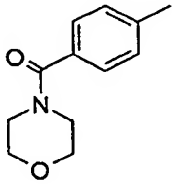
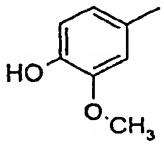
The compounds in the table below were prepared and purified according to the methods of Examples 53 – 92, except that the reactions were heated for 4 hours instead of overnight and 7-bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine was used in lieu of 8-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



| Example | Reagent | R | Measured Mass (M+H) |
|---|---|---|---|
| 205 | Furan-3-boronic acid |  | 393.1906 |
| 206 | Phenylboronic acid |  | 403.2107 |
| 207 | Thiophene-3-boronic acid |  | 409.1692 |
| 208 | 4-Methylphenylboronic acid |  | 417.2249 |
| 209 | 2-(Hydroxyphenyl)boronic acid |  | 419.2054 |
| 210 | 3-Hydroxyphenylboronic acid |  | 419.2074 |
| 211 | 3-Fluorophenylboronic acid |  | 421.2014 |
| 212 | 4-Fluorophenylboronic acid |  | 421.2009 |
| 213 | 2-Fluoropyridine-5-boronic acid |  | 422.1990 |
| 214 | (2-Hydroxymethylphenyl)boronic acid dehydrate |  | 433.2233 |
| 215 | 3-(Hydroxymethyl)phenylboronic acid |  | 433.2220 |

| | | | |
|---|---|---|---|
| 216 | 4-(Hydroxymethyl)phenylboronic acid |  | 433.2195 |
| 217 | 3-Aminophenylboronic acid monohydrate |  | 418.2204 |
| 218 | 3-Chlorophenylboronic acid |  | 437.1721 |
| 219 | 2-Chlorophenylboronic acid |  | 437.1715 |
| 220 | 4-Chlorophenylboronic acid |  | 437.1736 |
| 221 | 2,4-Difluorophenylboronic acid |  | 439.1952 |
| 222 | (3-Aminocarbonylphenyl)boronic acid |  | 446.2159 |
| 223 | 3-Carboxyphenylboronic acid |  | 447.2000 |
| 224 | 4-Carboxyphenylboronic acid |  | 447.2018 |
| 225 | [3-(3-Hydroxypropyl)phenyl]boronic acid |  | 461.2507 |
| 226 | 3,4-Dichlorophenylboronic acid |  | 471.1342 |

| | | | |
|---|---|---|---|
| 227 | 4-(2-Carboxyvinyl)phenylboronic acid |  | 473.2168 |
| 228 | 3-(*N*,*N*-Dimethylaminocarbonyl)phenylboronic acid |  | 474.2458 |
| 229 | 4-(Methanesulfonyl)phenylboronic acid |  | 481.1862 |
| 230 | 3-(*N*-Isopropylaminocarbonyl)phenylboronic acid |  | 488.2625 |
| 231 | 3-(*N*-Propylaminocarbonyl)phenylboronic acid |  | 488.2644 |
| 232 | 4-(Ethylsulfonyl)phenylboronic acid |  | 495.2034 |
| 233 | 3-(Methylsulfonylamino)phenylboronic acid |  | 496.1984 |
| 234 | 4-(Methylsulfonylamino)phenylboronic acid |  | 496.1982 |

| | | | |
|---|---|---|---|
| 235 | 3-(Pyrrolidine-1-carbonyl)phenylboronic acid |  | 500.2636 |
| 236 | 4-(Pyrrolidine -1-carbonyl)phenylboronic acid |  | 500.2630 |
| 237 | 4-(Isobutylaminocarbonyl)phenylboronic acid |  | 502.2810 |
| 238 | 3-(Morpholine-4-carbonyl)phenylboronic acid |  | 516.2607 |
| 239 | 4-(Morpholine-4-carbonyl)phenylboronic acid |  | 516.2592 |
| 240 | 2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol |  | 449.2159 |

Examples 241 – 277

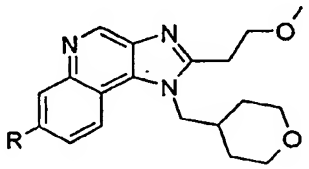
Part A

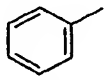
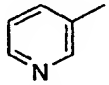
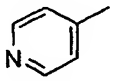
A solution of 3-methoxypropionyl chloride (4.37 g, 35.7 mmol) in dichloromethane (25 mL) was added to a solution of crude 7-bromo-$N^4$-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (32.5 mmol) in dichloromethane (350 mL). The reaction mixture was stirred for 30 minutes and then concentrated under reduced pressure. The resulting amide intermediate was slurried in ethanol (300 mL). A solution of

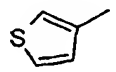
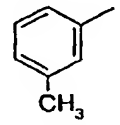
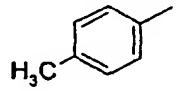
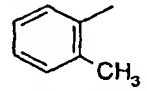
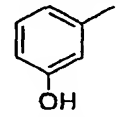
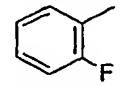
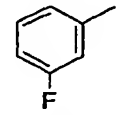
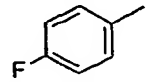
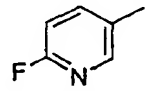
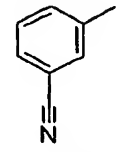
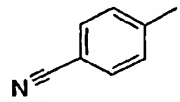
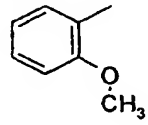
potassium carbonate (6.73 g, 49 mmol) in water (100 mL) was added, resulting in complete dissolution. The solution was heated at reflux overnight and then cooled to ambient temperature. The ethanol was removed under reduced pressure and the resulting aqueous slurry was extracted with dichloromethane (2 x 350 mL). The combined extracts were washed sequentially with water and brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide a red-violet solid. This material was purified by prep HPLC (silica gel eluted with a gradient of 1-10% CMA in chloroform) followed by recrystallization from acetonitrile to provide 6.5 g 7-bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a tan crystalline solid.

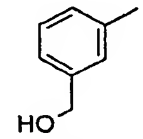
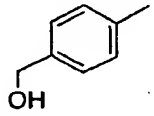
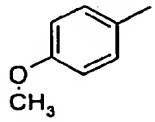
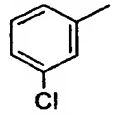
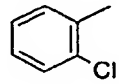
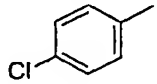
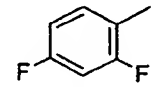
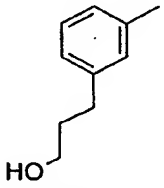
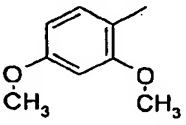
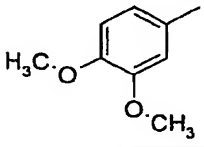
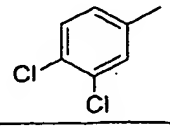
Part B

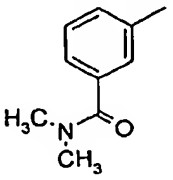
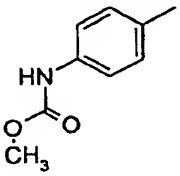
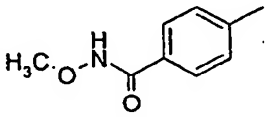
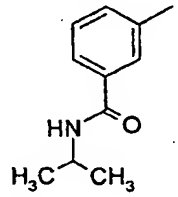
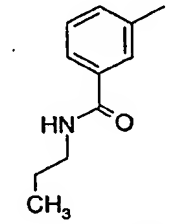
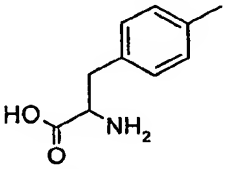
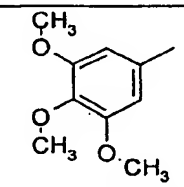
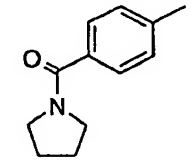
The compounds in the table below were prepared and purified according to the methods of Examples 53 – 92, except that the reactions were heated for 4 hours instead of overnight and 7-bromo-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was used in lieu of 8-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

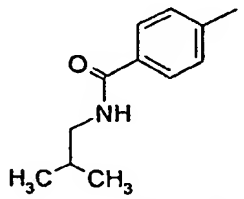
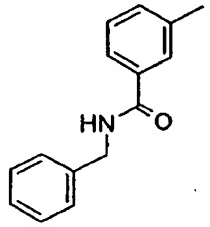
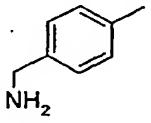


| Ex | Reagent | R | Measured Mass (M+H) |
|---|---|---|---|
| 241 | Phenylboronic acid |  | 402.2170 |
| 242 | Pyridine-3-boronic acid |  | 403.2115 |
| 243 | Pyridine-4-boronic acid |  | 403.2098 |

| | | | |
|---|---|---|---|
| 244 | Thiophene-3-boronic acid |  | 408.1740 |
| 245 | 3-Methylphenylboronic acid |  | 416.2302 |
| 246 | 4-Methylphenylboronic acid |  | 416.2305 |
| 247 | *o*-Tolylboronic acid |  | 416.2303 |
| 248 | 3-Hydroxyphenylboronic acid |  | 418.2090 |
| 249 | 2-Fluorophenylboronic acid |  | 420.2052 |
| 250 | 3-Fluorophenylboronic acid |  | 420.2065 |
| 251 | 4-Fluorophenylboronic acid |  | 420.2058 |
| 252 | 2-Fluoropyridine-5-boronic acid |  | 421.2027 |
| 253 | 3-Cyanophenylboronic acid |  | 427.2146 |
| 254 | 4-Cyanophenylboronic acid |  | 427.2105 |
| 255 | 2-Methoxyphenylboronic acid |  | 432.2287 |

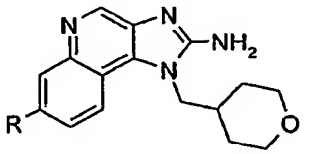
| | | | |
|---|---|---|---|
| 256 | 3-(Hydroxymethyl)phenylboronic acid |  | 432.2268 |
| 257 | 4-(Hydroxymethyl)phenylboronic acid |  | 432.2267 |
| 258 | 4-Methoxyphenylboronic acid |  | 432.2270 |
| 259 | 3-Chlorophenylboronic acid |  | 436.1756 |
| 260 | 2-Chlorophenylboronic acid |  | 436.1763 |
| 261 | 4-Chlorophenylboronic acid |  | 436.1775 |
| 262 | 2,4-Difluorophenylboronic acid |  | 438.1998 |
| 263 | [3-(3-Hydroxypropyl)phenyl]boronic acid |  | 460.2587 |
| 264 | 2,4-Dimethoxyphenylboronic acid |  | 462.2371 |
| 265 | 3,4-Dimethoxyphenylboronic acid |  | 462.2380 |
| 266 | 3,4-Dichlorophenylboronic acid |  | 470.1409 |

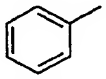
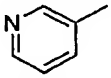
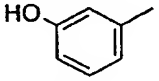
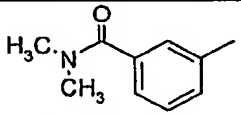
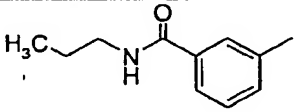
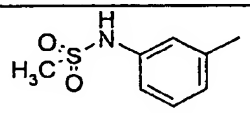
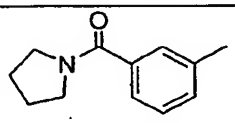
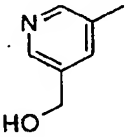
| | | | |
|---|---|---|---|
| 267 | 3-(*N*,*N*-Dimethylaminocarbonyl)phenylboronic acid |  | 473.2558 |
| 268 | 4-(Methoxycarbonylamino)phenylboronic acid |  | 475.2341 |
| 269 | 4-(*O*-Methylhydroxylaminocarbonyl)phenylboronic acid |  | 475.2339 |
| 270 | 3-(*N*-Isopropylaminocarbonyl)phenylboronic acid |  | 487.2661 |
| 271 | 3-(*N*-Propylaminocarbonyl)phenylboronic acid |  | 487.2679 |
| 272 | 4-Borono-*DL*-phenylalanine |  | 489.2482 |
| 273 | 3,4,5-Trimethoxyphenylboronic acid |  | 492.2477 |
| 274 | 4-(Pyrrolidine-1-carbonyl)phenylboronic acid |  | 499.2718 |

| | | | |
|---|---|---|---|
| 275 | 4-(Isobutylaminocarbonyl)phenylboronic acid |  | 501.2862 |
| 276 | 3-(*N*-Benzylaminocarbonyl)phenylboronic acid |  | 535.2708 |
| 277 | (4-Aminomethylphenyl)boronic acid, pincacol ester, HCl |  | 431.2430 |

Examples 278 – 285

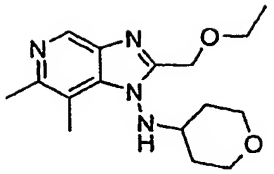
A solution of 7-bromo-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-amine (18 mg, 0.10 mmol) in 7:3 volume:volume (v:v) chloroform:methanol (2 mL) was added to a test tube, and the solvent was removed by vacuum centrifugation. The boronic acid (0.11 mmol) indicated in the table below and *n*-propanol (1.6 mL) were sequentially added. The test tube was purged with nitrogen. Palladium (II) acetate (150 µL of a 4 mg/mL solution in toluene, 0.0026 mmol), 2 M aqueous sodium carbonate solution (600 µL), deionized water (63 µL), and a solution of 0.15 mol% triphenylphosphine in *n*-propanol (53 µL, 0.0078 mmol) were sequentially added. The test tube was purged with nitrogen, capped, and then heated at 80 °C overnight in a sand bath. Palladium (II) acetate (150 µL of a 4 mg/mL solution in toluene, 0.0026 mmol) was added and the tubes were heated for an additional 4 hours. For Example 285, glacial acetic acid (500 µL), trifluoroacetic acid (500 µL), and deionized water (500 µL) were added to the test tube. The reaction was heated for 4 hours at 60 °C. The reaction mixtures were purified according to the methods of Examples 53 – 92. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



| Example | Reagent | R | Measured Mass (M+H) |
|---|---|---|---|
| 278 | Phenylboronic acid |  | 359.1869 |
| 279 | Pyridine-3-boronic acid |  | 360.1836 |
| 280 | 3-Hydroxyphenylboronic acid |  | 375.1826 |
| 281 | 3-(*N*,*N*-Dimethylaminocarbonyl)phenylboronic acid |  | 430.2254 |
| 282 | 3-(*N*-Propylaminocarbonyl)phenylboronic acid |  | 444.2399 |
| 283 | 3-(Methylsulfonylamino)phenylboronic acid |  | 452.1773 |
| 284 | 3-(Pyrrolidine-1-carbonyl)phenylboronic acid |  | 456.2401 |
| 285 | 5-(*tert*-butyldimethylsilanyloxy-methyl)pyridine-3-boronic acid |  | 390.1932 |

Compound 5

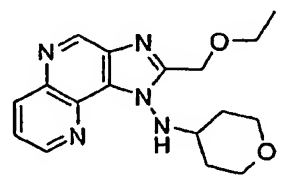
2-Ethoxymethyl-6,7-dimethyl-*N*-(tetrahydropyran-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-1-amine



Under a nitrogen atmosphere, 4-chloro-2-ethoxymethyl-6,7-dimethyl-*N*-(tetrahydropyran-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-1-amine (1.00 g, 1 eq) was combined with ammonium formate (1.94 g, 10.5 eq), methanol (40 mL) and ethanol (80 mL). The mixture was flushed with nitrogen for several minutes, 10% palladium on carbon (1.00 g) was added, and then the reaction mixture was heated to 80 °C for 3 hours. The reaction mixture was allowed to cool to ambient temperature and then it was filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure. The residue was partitioned between 5% sodium hydroxide (100 mL) and dichloromethane (100 mL). The aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organics were dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel eluting with 3% methanol in chloroform) to provide 0.52 g of a clear oil which slowly solidified. This material was dried under vacuum at 40 °C for 16 hours to provide 0.52 g of 2-ethoxymethyl-6,7-dimethyl-*N*-(tetrahydropyran-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-1-amine as a white solid, mp 94-97 °C. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 5.46 (d, $J$ = 3.2 Hz, 1H), 4.87 (br s, 2H), 4.00 (m, 2H), 3.63 (q, $J$ = 7.0 Hz, 2H), 3.45-3.25 (m, 3H), 2.68 (s, 3H), 2.60 (s, 3H), 1.77-1.44 (m, 4H), 1.26 (t, $J$ = 7.0 Hz, 3H); MS (APCI) *m/z* 305 $(M + H)^+$; Anal. Calcd for $C_{16}H_{24}N_4O_2 \cdot 0.50\ H_2O$: C, 61.32; H, 8.04; N, 17.88. Found: C, 60.92; H, 7.93; N, 17.75.

Compound 6

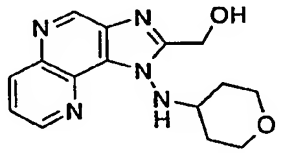
2-Ethxoymethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-amine



2-Ethxoymethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-amine was prepared as described in Example 36 of International Publication No. WO 06/026760.

Compound 7

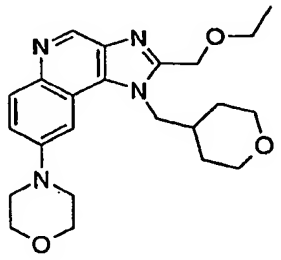
[1-(Tetrahydro-2*H*-pyran-4-yl)amino-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methanol



Under a nitrogen atmosphere boron tribromide (2.00 mL of 1 M in dichloromethane, 2 eq) was added dropwise to a chilled (ice water bath) solution of 2-ethxoymethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-amine (0.327 g, 1 eq) in dichloromethane (10 mL). The reaction was allowed to slowly come to ambient temperature and was stirred overnight. After 18 hours the reaction was quenched with the dropwise addition of water (2 mL) and methanol (10 mL) was added. The dichloromethane and methanol were removed under reduced pressure to provide an aqueous slurry. A solution of ammonia in methanol (10 mL of 7 M) was added and the mixture was stirred for 1 hour. Silica gel (3 g) was added and the slurry was loaded on a prep HPLC column which was then eluted with a gradient of 1 – 30 % CMA in chloroform to provide a yellow solid. The solid was purified by prep HPLC (40 g of silica gel eluted with a gradient of 1 – 25% CMA in chloroform) to provide 15 mg of a light yellow solid. This material was recrystallized from acetonitrile to provide 5 mg of [1-(tetrahydro-2*H*-pyran-4-yl)amino-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methanol as light yellow crystals, mp 203–205 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.26 (s, 1 H), 9.04 (dd, $J$ = 4.2, 1.6 Hz, 1 H), 8.53 (dd, $J$ = 8.5, 1.6 Hz, 1 H), 7.76 (dd, $J$ = 8.5, 4.2 Hz, 1 H), 6.96 (d, $J$ = 2.5 Hz, 1 H), 5.56 (t, $J$ = 6.1 Hz, 1 H), 4.83 (d, $J$ = 6.1 Hz, 2 H), 3.88-3.82 (m, 2 H), 3.82-3.75 (m, 1 H), 3.24-3.20 (m, 2 H), 1.65 (br, 2 H), 1.57-1.50 (m, 2 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 156.1, 149.6, 145.5, 138.7, 137.3, 137.1, 134.3, 132.1, 122.5, 65.2, 56.4, 54.7, 30.6; MS (APCI) *m/z* 300.17 $(M + H)^+$; Anal. Calcd for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72; N, 23.40; Found: C, 59.91; H, 5.41; N, 23.05.

Example 286

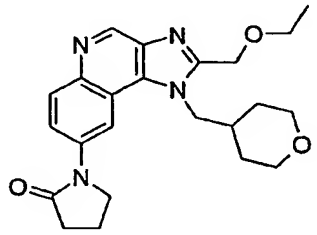
2-(Ethoxymethyl)-8-morpholin-4-yl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline



Under a nitrogen atmosphere, toluene (2.50 mL) was added to a vial containing 8-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.45 g, 1.11 mmol), morpholine (0.12 mL, 1.33 mmol), tris(dibenzylideneacetone)dipalladium (35 mg, 0.033 mmol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (42 mg, 0.0664 mmol), and sodium *tert*-butoxide (0.15 g, 1.55 mmol). Nitrogen was bubbled through the mixture. The vial was sealed with a TEFLON lined cap and then heated at 80 °C for 20 hours. The reaction mixture was diluted with chloroform (2 mL) and then filtered through a cotton plug. The filtrate was concentrated under reduced pressure to provide an orange solid. The solid was purified by prep HPLC (silica gel eluted with a gradient of 0-25% CMA in chloroform) to provide an off-white solid. This material was recrystallized from ethyl acetate/heptane to provide 178 mg of 2-ethoxymethy-8-(morpholin-4-yl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as an off-white solid, mp 167-170 °C; $^1$H NMR (500 MHz, $d_6$-DMSO) δ 8.94 (s, 1H), 8.00 (d, $J$ = 9.2, 1H), 7.54 (dd, $J$ = 9.1, 2.9, 1H), 7.43 (d, $J$ = 2.8, 1H), 4.80 (s, 2H), 4.62 (d, $J$ = 7.3, 2H), 3.81 (m, 6H), 3.57 (q, $J$ = 6.9, 2H), 3.32 (m, 4H), 3.16 (td, $J$ = 11.3, 1.9, 2H), 2.25 (m, 1H), 1.50 (qd, $J$ = 12.9, 4.4, 2H), 1.47 (m, 2H), 1.15 (t, $J$ = 7.0, 3H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 151.4, 149.0, 141.6, 139.1, 136.4, 132.8, 130.9, 118.4, 102.5, 66.5, 66.0, 65.4, 64.3, 50.5, 48.4, 36.0, 29.9, 14.9; Anal. calcd for $C_{23}H_{30}N_4O_3$: C, 67.29; H, 7.37; N, 13.65. Found: C, 67.46; H, 7.19; N, 13.78.

Example 287

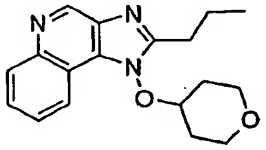
1-[2-(Ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-8-yl]pyrrolidin-2-one



Under a nitrogen atmosphere, toluene (2.50 mL) was added to a vial containing 8-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.45 g, 1.11 mmol), 2-pyrrolidinone (0.10 mL, 1.33 mmol), tris(dibenzylideneacetone)dipalladium (35 mg, 0.033 mmol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (42 mg, 0.066 mmol), and sodium *tert*-butoxide (0.15 g, 1.55 mmol). Nitrogen was bubbled through the mixture. The vial was capped with a TEFLON lined cap and then heated at 80 °C for 20 hours. The reaction mixture was diluted with chloroform (2 mL) and then filtered through a cotton plug. The filtrate was concentrated under reduced pressure to provide a green solid. The solid was purified by prep HPLC (silica gel eluted with a gradient of 0-25% CMA in chloroform) to provide an off-white solid. This material was recrystallized from ethyl acetate/heptane to provide 65 mg of 1-[2-ethoxymethy-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-8-yl]pyrrolidin-2-one as an off-white solid, mp 152-155 °C; $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.10 (s, 1H), 8.90 (d, $J$ = 2.2, 1H), 8.16 (d, $J$ = 9.1, 1H), 7.90 (d, $J$ = 9.2, 2.2, 1H), 4.80 (s, 2H), 4.58 (d, $J$ = 7.6, 2H), 4.04 (t, $J$ = 7.2, 2H), 3.81 (t, $J$ = 11.1, 2H), 3.59 (q, $J$ = 6.9, 2H), 3.16 (m, 2H), 2.60 (t, $J$ = 8.2, 2H), 2.34 (m, 1H), 2.14 (quin, $J$ = 7.6, 2H), 1.49 (m, 4H), 1.16 (t, $J$ = 6.9, 3H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 174.5, 151.7, 143.8, 140.8, 137.6, 136.2, 133.2, 130.6, 119.2, 117.5, 109.5, 66.6, 65.5, 64.3, 50.6, 48.2, 35.5, 32.5, 29.7, 17.4, 14.9; Anal. calcd for $C_{23}H_{28}N_4O_3$: C, 67.63; H, 6.91; N, 13.72. Found: C, 67.47; H, 6.87; N, 13.62.

Example 288

2-Propyl-1-(tetrahydro-2*H*-pyran-4-yloxy)-1*H*-imidazo[4,5-*c*]quinoline



Part A

*N*-(4-Chloroquinolin-3-yl)butyramide (8.4 g, 33.8 mmol), *O*-benzylhydroxylamine hydrochloride (7.0 g, 43.9 mmol), and isopropanol (100 mL) were combined and then heated at 60 °C for 7 hours. The reaction mixture was allowed to cool to ambient temperature and a precipitate formed. The supernatant was decanted off. The precipitate was partitioned between dichloromethane (100 mL) and saturated aqueous sodium carbonate (50 mL). The layers were separated and the organic layer was washed with water (2 x 25 mL), dried over potassium carbonate, filtered, and then concentrated under reduced pressure to provide 7.3 g of 1-benzyloxy-2-propyl-1*H*-imidazo[4,5-*c*]quinoline as a dark oil which started to crystallize on standing.

Part B

A mixture of the material from Part A (23 mmol), 10% palladium on carbon (0.50 g), and ethanol (90mL) was placed under hydrogen pressure (30 psi, 2.1 X $10^5$ Pa) for 3 hours. The reaction mixture was filtered through a layer of CELITE filter agent. The filtrate was diluted with dichloromethane (25 mL) and a precipitate formed. The precipitate was isolated by filtration to provide 1.6 g of 2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-ol. The filtrate was concentrated under reduced pressure to obtain additional product.

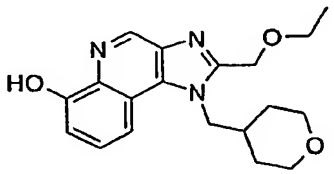
Part C

2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-ol (0.4 g, 1.8 mmol), 4-chlorotetrahydropyran (0.4 g, 3.3 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.4 g, 2.6 mmol) were combined in a pressure vessel. The vessel was sealed and then heated in an oven at 120 °C for 22 hours. The reaction was repeated on a larger scale (x8). The small and larger scale reaction mixtures were combined and then partitioned between dichloromethane (150 mL) and saturated aqueous sodium carbonate (25 mL). The organic layer was separated, washed with water (3 x 25 mL), dried over potassium carbonate,

filtered, and then concentrated under reduced pressure to provide 4.8 g of crude product as a brown oil. This material was purified by column chromatography (silica gel eluted with 5% methanol in dichloromethane containing 5 mL of ammonium hydroxide per liter of dichloromethane) to provide 0.98 g of 2-propyl-1-(tetrahydro-2*H*-pyran-4-yloxy)-1*H*-imidazo[4,5-*c*]quinoline as a yellow oil. HRMS (ESI) calcd for $C_{18}H_{21}N_3O_2 + H^+$: 312.1712, found 312.1712.

Example 289

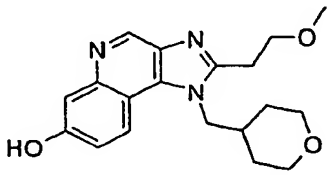
2-(Ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-6-ol



A solution of 6-(benzyloxy)-2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (407 mg, 0.943 mmol), prepared as described in Example 13, in 45% HBr in acetic acid (10 mL) was heated at 65 °C for 1.5 hours. The reaction mixture was cooled in an ice bath and was adjusted slowly to pH 7 with 50% aqueous sodium hydroxide solution. A pale brown precipitate was isolated by filtration, washed, and dried. The solid was recrystallized from boiling hexanes/ethyl acetate (15 mL) to yield 117 mg of 2-(ethoxymethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-6-ol as grey needles, mp 173-177 °C. Anal. calcd for $C_{19}H_{23}N_3O_3 \cdot 0.20\ H_2O$: C, 66.15; H, 6.84; N, 12.18. Found: C, 66.13; H, 6.84; N, 12.02.

Example 290

2-(2-Methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-ol

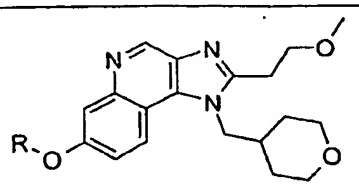


A mixture of 7-(benzyloxy)-2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (1.00 g, 2.32 mmol, prepared as described in Example 51), 10% palladium hydroxide on carbon (0.1 g), and ethanol (20 mL) was hydrogenated for 18 hours using a Parr apparatus. The mixture was filtered through

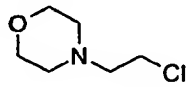
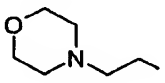
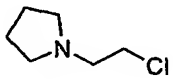
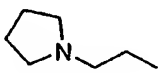
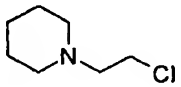
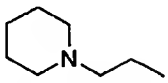
CELITE filter agent and the filtrate was concentrated under reduced pressure. The resulting oil was purified by prep HPLC (silica gel eluted with 0-35% CMA in chloroform) to yield an off-white solid. The solid was suspended in boiling acetonitrile (20 mL), filtered, washed with cold acetonitrile, and dried to afford 0.429 g of 2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-ol as white needles, mp 242-245 °C. Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.72; H, 6.68; N, 12.22.

Examples 291-293

A mixture of 2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-ol (0.75 g, 2.2 mmol, prepared as described in Example 290), cesium carbonate (3.59 g, 11 mmol), and DMF (20 mL) was heated at 75 °C for 30 minutes. A reagent (2.75 mmol) from the Table below was added to the mixture, which was then heated between 17 and 23 hours. The DMF was removed under reduced pressure at 65 °C. The residue was partitioned between chloroform (100 mL) and water (100 mL). The organic layer was separated and washed with brine (50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude oil was purified by prep HPLC (silica gel eluted with 10-35% CMA in chloroform) to yield a pale yellow solid. The solid was dissolved in eathanol (10 mL) and anhydrous hydrogen chloride in ethanol was added (3.0 M, about 5 mL). The solution was stirred at room temperature for 15 minutes. The solvent was removed under reduced pressure and the pale yellow solid was suspended in cold ethanol (about 15 mL). The solid was isolated by filtration, washed with cold ethanol, and dried to afford the hydrochloride salts of the structures shown in the Table below.



| Example | Reagent | R |
|---|---|---|

| | | |
|---|---|---|
| 291 |  |  |
| 292 |  |  |
| 293 |  |  |

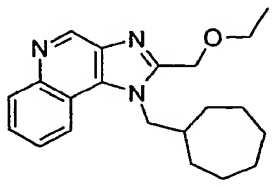
Example 291: 576 mg of 2-(2-methoxyethyl)-7-(2-morpholin-4-ylethoxy)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was isolated as beige needles, mp 220-224 °C. Anal. calcd for $C_{25}H_{34}N_4O_4 \cdot 2.40$ HCl: C, 55.39; H, 6.77; N, 10.34. Found: C, 55.41; H, 6.97; N, 10.19.

Example 292: 273 mg of 2-(2-methoxyethyl)-7-(2-pyrrolidin-1-ylethoxy)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was isolated as brown needles, mp 205-209 °C. Anal. calcd for $C_{26}H_{36}N_4O_3 \cdot 3.25$ HCl: C, 54.68; H, 6.93; N, 9.81. Found: C, 54.68; H, 6.84; N, 9.66.

Example 293: 401 mg of 2-(2-methoxyethyl)-7-(2-piperidin-1-ylethoxy)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline was isolated as brown needles, mp 205-209 °C. Anal. calcd for $C_{26}H_{36}N_4O_3 \cdot 3.25$ HCl: C, 54.68; H, 6.93; N, 9.81. Found: C, 54.68; H, 6.84; N, 9.66.

Example 294

1-(Cycloheptylmethyl)-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline



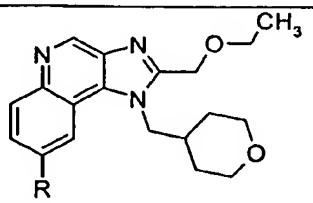
A mixture of cycloheptyl cyanide (3.00 mL, 22.5 mmol), 10% palladium on carbon (0.42 g), and 3 M hydrogen chloride in ethanol (45 mL) was hydrogenated on a Parr apparatus overnight. Platinum oxide (0.10 g) was added to the reaction mixture, which was then hydrogenated on a Parr apparatus for 4 hours. The reaction mixture was filtered through CELITE filter agent, which was rinsed afterwards with ethanol. The filtrate was

concentrated to yield a solid that was treated with diethyl ether (50 mL). A white solid was isolated by filtration and was dried to provide 1.57 g of 1-cycloheptylmethanamine hydrochloride.

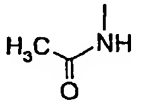
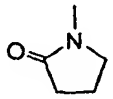
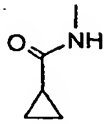
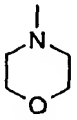
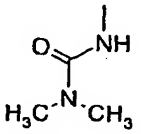
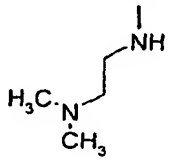
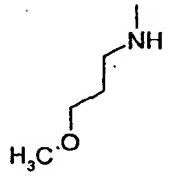
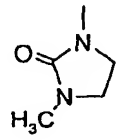
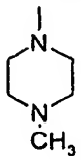
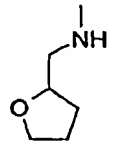
1-(Cycloheptylmethyl)-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline was prepared according to the general methods of Example 27 using 1-cycloheptylmethanamine hydrochloride in lieu of (*S*)-(+)-tetrahydrofurfurylamine in Part A, and palladium on carbon (10% w/w) as the catalyst and methanol/acetontrile as the solvent in Part B. The crude product was purified by prep HPLC (silica gel eluted with a gradient of 1-15%% CMA in chloroform) to provide a yellow oil. The oil was dissolved in methanol/chloroform and treated with about 0.25 g of activated carbon for 2 hours. The mixture was filtered through CELITE filter agent and the filtrate was concentrated and dried to yield 1-(cycloheptylmethyl)-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline as a yellow oil; Anal. Calcd for $C_{21}H_{27}N_3O \cdot 0.2CH_4O$: C, 74.05; H, 8.15; N, 12.22; Found: C, 73.84; H, 8.13; N, 12.17.

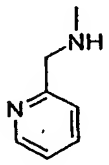
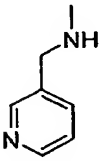
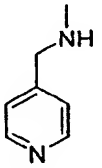
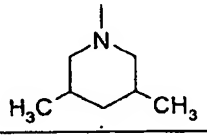
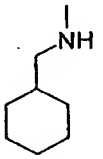
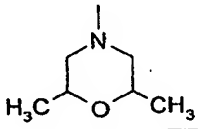
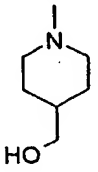
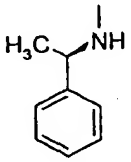
Examples 295-320

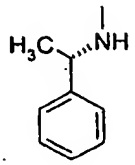
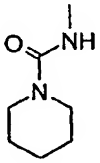
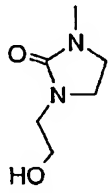
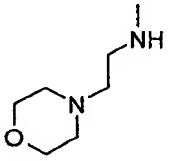
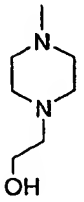
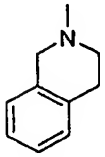
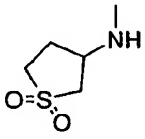
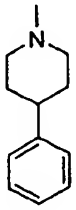
A toluene solution (250 µL) containing 8-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (prepared as described in Example 6) (40 mg, 0.10 mmol), tris(dibenzylideneacetone)dipalladium(0) (5.6 mg, 0.06 equivalents), and (+/-)-2,2'-bis(diphenylphosphino)-1,1'-binapthalene (7.6 mg, 0.12 equivalents) was added to a test tube containing 1 M potassium *tert*-butoxide in THF (150 µL) and one of the reagents (1.5 equivalents) listed in the table below. The test tube was purged with nitrogen, capped, and then heated at 80 °C overnight in a sand bath. The solvent was removed on a vacuum centrifuge and the product was purified as described above in Examples 53-92. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.




| Example | Reagent | R | Measured Mass |
|---|---|---|---|

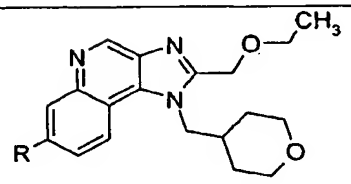
| | | | (M+H) |
|---|---|---|---|
| 295 | Acetamide |  | 383.2085 |
| 296 | 2-Pyrrolidone |  | 409.2206 |
| 297 | Cyclopropyanecarboxamide |  | 409.2233 |
| 298 | Morpholine |  | 411.2355 |
| 299 | 1,1-Dimethylurea |  | 412.2338 |
| 300 | *N,N*-Dimethylethylenediamine |  | 412.2702 |
| 301 | 3-Methoxypropylamine |  | 413.2518 |
| 302 | 1-Methyl-2-imidazolidinone |  | 424.2321 |
| 303 | 1-Methylpiperazine |  | 424.2677 |
| 304 | Tetrahydrofurfurylamine |  | 425.2547 |

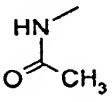
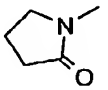
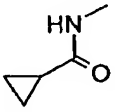
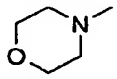
| | | | |
|---|---|---|---|
| 305 | 2-(Aminomethyl)pyridine |  | 432.2416 |
| 306 | 3-Picolylamine |  | 432.2394 |
| 307 | 4-Picolylamine |  | 432.2442 |
| 308 | 3,5-Dimethylpiperidine |  | 437.2884 |
| 309 | Aminomethylcyclohexane |  | 437.2878 |
| 310 | 2,6-Dimethylmorpholine |  | 439.2697 |
| 311 | 4-(Hydroxymethyl)piperidine |  | 439.2683 |
| 312 | (*R*)-(+)-1-Phenylethylamine |  | 445.2570 |

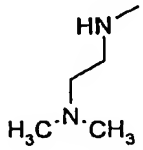
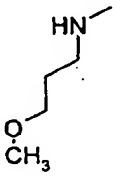
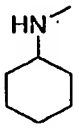
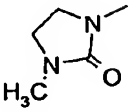
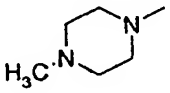
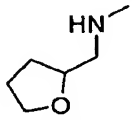
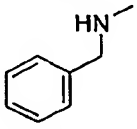
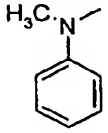
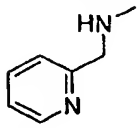
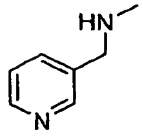
| | | | |
|---|---|---|---|
| 313 | (*S*)-(-)-1-Phenylethylamine |  | 445.2570 |
| 314 | 1-Carbamylpiperidine |  | 452.2629 |
| 315 | 1-(2-Hydroxyethyl)-2-imidazolidinone |  | 454.2412 |
| 316 | 4-(2-Aminoethyl)morpholine |  | 454.2796 |
| 317 | *N*-(2-Hydroxyethyl)piperazine |  | 454.2816 |
| 318 | 1,2,3,4-Tetrahydroisoquinoline |  | 457.2572 |
| 319 | 1,1-Dioxidotetrahydrothien-3-ylamine |  | 459.2025 |
| 320 | 4-Phenylpiperidine |  | 485.2876 |

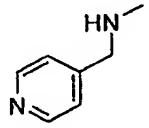
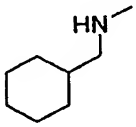
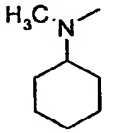
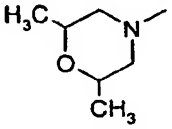
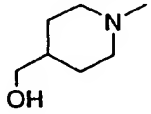
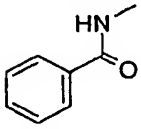
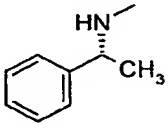
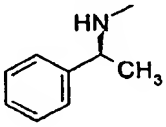
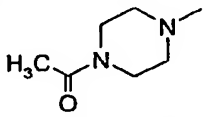
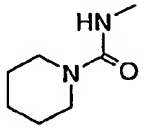
Examples 321-350

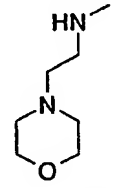
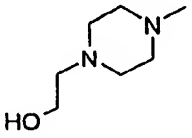
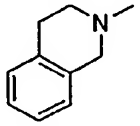
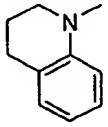
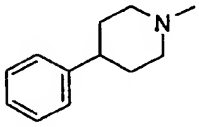
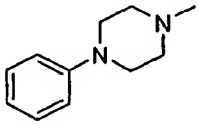
A toluene solution (250 μL) containing 7-bromo-2-ethoxymethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (prepared as described in Examples 129-157) (40 mg, 0.10 mmol), tris(dibenzylideneacetone)dipalladium(0) (3.3 mg, 0.03 equivalents), and (+/-)-2,2'-bis(diphenylphosphino)-1,1'-binapthalene (4.0 mg, 0.06 equivalents) was added to a test tube containing 1 M potassium *tert*-butoxide in THF (150 μL) and one of the reagents (1.2 equivalents) listed in the table below. The test tube was purged with nitrogen, capped, and then heated at 80 °C overnight in a sand bath. A toluene solution (250 μL) containing tris(dibenzylideneacetone)dipalladium(0) (3.3 mg, 0.03 equivalents) and (+/-)-2,2'-bis(diphenylphosphino)-1,1'-binapthalene (4.0 mg, 0.06 equivalents) was added to each test tube. The test tube was purged with nitrogen, capped, and then heated at 80 °C overnight in a sand bath. The solvent was removed on a vacuum centrifuge and the product was purified as described above in Examples 53-92. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



| Example | Reagent | R | Measured Mass (M+H) |
|---|---|---|---|
| 321 | Acetamide |  | 383.2081 |
| 322 | 2-Pyrrolidone |  | 409.2197 |
| 323 | Cyclopropanecarboxamide |  | 409.2232 |
| 324 | Morpholine |  | 411.2372 |

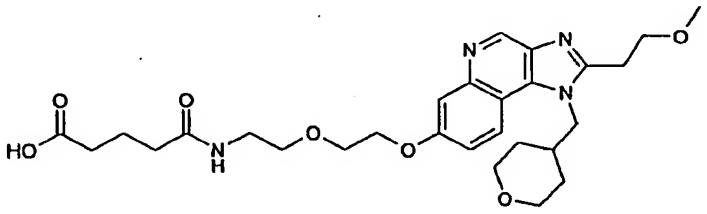
| | | | |
|---|---|---|---|
| 325 | *N,N*-Dimethylethylenediamine |  | 412.2680 |
| 326 | 3-Methoxypropylamine |  | 413.2531 |
| 327 | Cyclohexylamine |  | 423.2738 |
| 328 | 1-Methyl-2-imidazolidinone |  | 424.2351 |
| 329 | 1-Methylpiperazine |  | 424.2695 |
| 330 | Tetrahydrofurfurylamine |  | 425.2585 |
| 331 | Benzylamine |  | 431.2417 |
| 332 | *N*-Methylaniline |  | 431.2426 |
| 333 | 2-(Aminomethyl)pyridine |  | 432.2358 |
| 334 | 3-Picolylamine |  | 432.2364 |

| | | | |
|---|---|---|---|
| 335 | 4-Picolylamine |  | 432.2362 |
| 336 | Aminomethylcyclohexane |  | 437.2911 |
| 337 | *N*-Methylcyclohexylamine |  | 437.2877 |
| 338 | 2,6-Dimethylmorpholine |  | 439.2698 |
| 339 | 4-(Hydroxymethyl)piperidine |  | 439.2688 |
| 340 | Benzamide |  | 445.2212 |
| 341 | (*R*)-(+)-1-Phenylethylamine |  | 445.2561 |
| 342 | (*S*)-(-)-1-Phenylethylamine |  | 445.2571 |
| 343 | 1-Acetylpiperazine |  | 452.2667 |
| 344 | 1-Carbamylpiperidine |  | 452.2635 |

| | | | |
|---|---|---|---|
| 345 | 4-(2-Aminoethyl)morpholine |  | 454.2778 |
| 346 | *N*-(2-Hydroxyethyl)piperazine |  | 454.2782 |
| 347 | 1,2,3,4-Tetrahydroisoquinoline |  | 457.2596 |
| 348 | 1,2,3,4-Tetrahydroquinoline |  | 457.2556 |
| 349 | 4-Phenylpiperidine |  | 485.2935 |
| 350 | 1-Phenylpiperazine |  | 486.2866 |

Example 351

5-{[2-(2-{[2-(2-Methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxy}ethoxy)ethyl]amino}-5-oxopentanoic acid



Part A

A stirring solution of 2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-ol (2.00 g, 5.86 mmol), *tert*-butyl 2-(2-hydroxyethoxy)ethylcarbamate (1.38 g, 6.74 mmol) and triphenylphosphine (1.77 g, 6.74

mmol) in tetrahydrofuran (40 mL) was placed under an atmosphere of nitrogen and cooled to 0 °C. Diisopropyl azodicarboxylate (1.3 mL, 6.74 mmol) was added dropwise over 5 minutes via syringe. The resulting solution was allowed to warm to ambient temperature and stirred overnight. After 26 hours, the volatiles were removed under reduced pressure and the resulting residue was purified by column chromatography using a HORIZON HPFC system (silica cartridge, eluting with 0 – 35% CMA-80/chloroform). The product containing fractions were combined and concentrated under reduced pressure to yield 2.77g of *tert*-butyl 2-(2-{[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxy}ethoxy)ethylcarbamate as a light brown solid.

Part B

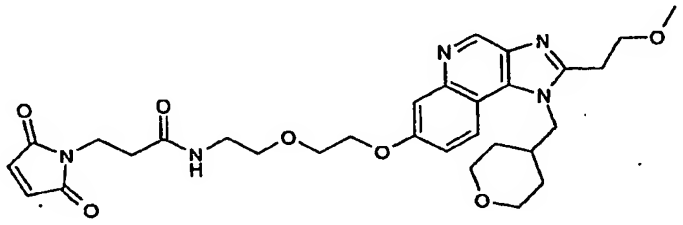
3 M HCl in ethanol (5.1 mL, 15.2 mmol) was added dropwise to a stirring solution of *tert*-butyl 2-(2-{[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxy}ethoxy)ethylcarbamate (2.67 g, 5.05 mmol) in ethanol (25 mL). The resulting solution was stirred at reflux 2 hours, cooled to ambient temperature and concentrated under reduced pressure to yield 2.54 g of 2-(2-{[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxy}ethoxy)ethanamine hydrochloride as a brown foam.

Part C

Glutaric anhydride (0.14 g, 1.20 mmol) was added to a stirring solution of 2-(2-{[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxy}ethoxy)ethanamine hydrochloride (0.50 g, 0.997 mmol) in pyridine (2 mL) at ambient temperature. After 18 hours, the solution was concentrated under reduced pressure and the resulting residue dissolved in water (10 mL). The pH was adjusted to 10 with 1 M sodium carbonate (aq) and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with dichloromethane (1 x 20 mL) and ethyl acetate (2 x 20 mL) and the organic layers were discarded. The pH of the aqueous layer was adjusted to 4 with 6 M HCl (aq) and extracted with dichloromethane (2 x 30 mL) and ethyl acetate (1 x 30 mL). The combined organic extracts were dried over MgSO4, filtered, and concentrated under reduced pressure to yield 332 mg of 5-{[2-(2-{[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxy}ethoxy)ethyl]amino}-5-oxopentanoic acid as a tan foam. Anal. calcd for $C_{28}H_{38}N_4O_7 \cdot 0.8H_2O$: C, 60.37; H, 7.17; N, 10.06. Found: C, 60.49; H, 6.96; N, 9.77.

Example 352

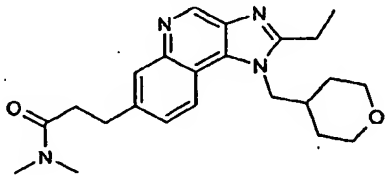
3-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*-[2-(2-{[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxy}ethoxy)ethyl]propanamide



1-{3-[(2,5-dioxopyrrolidin-1-yl)oxy]-3-oxopropyl}-1*H*-pyrrole-2,5-dione (0.156 g, 0.588 mmol) was added to a stirring solution of 2-(2-{[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxy}ethoxy)ethanamine (0.229 g, 0.534 mmol) in dichloromethane (6 mL) at ambient temperature. After 21 hours, the solution was loaded directly onto a 2 mm silica gel plate and purified by radial chromatography; eluting with 5% methanol in dichloromethane. The product containing fractions were combined and concentrated to yield 200 mg of 3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-*N*-[2-(2-{[2-(2-methoxyethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]oxy}ethoxy)ethyl]propanamide as a light yellow foam. Anal. calcd for $C_{30}H_{37}N_5O_7 \cdot H_2O$: C, 60.29; H, 6.58; N, 11.72. Found: C, 59.94; H, 6.73; N, 12.03.

Example 353

3-[2-Ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-*N*,*N*-dimethylpropanamide



Part A

A thick walled glass vessel, equipped with stir bar, was charged with a warmed solution of 7-bromo-2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (0.56 g, 1.5 mmol) in *N*,*N*-dimethylformamide (10 mL). To this solution was added in succession a solution of palladium acetate (0.1 eq., 37 mg, 0.15 mmol) and tri-

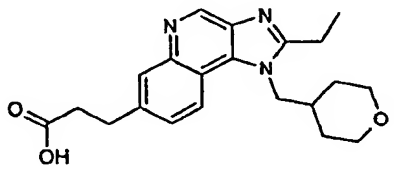
ortho-tolylphosphine (0.2 eq., 91 mg, 0.3 mmol) in *N,N*-dimethylformamide (5 mL); triethylamine (3.0 eq. , 0.6 mL); and a solution of *N,N*-dimethylacrylamide (1.2 eq., 178 mg, 1.8 mmol) in *N,N*-dimethylformamide (2 mL). The reaction mixture was purged with nitrogen and the vessel was sealed and heated to 120 °C for 18 hours. The reaction vessel was cooled to ambient temperature. The reaction mixture was transferred to a round bottom flask and concentrated to dryness under reduced pressure. The residue was treated with water and 10% NaOH, adjusting to pH=12. The mixture was then extracted with dichloromethane. The organic fractions were combined, dried ($MgSO_4$) and concentrated to dryness. Purification of the residue with a HORIZON HPFC system (silica cartridge, 0-15% CMA/chloroform) followed by recrystallization from acetonitrile provided 0.54 g of (2*E*)-3-[2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-*N,N*-dimethylprop-2-enamide as a white crystalline solid, mp 235-237 °C. MS (APCI) *m/z* 393 $(M + H)^+$; Anal. Calcd for $C_{23}H_{28}N_4O_2$: C, 70.38; H, 7.19; N, 14.27. Found: C, 70.29; H, 7.12; N, 14.28.

Part B

A glass Parr bottle (500 mL) was charged with 10% palladium on carbon (0.1 g) wetted with ethanol (5 mL) and a solution of (2*E*)-3-[2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-*N,N*-dimethylprop-2-enamide (0.5 g, 1.27 mmol) in methanol (250 mL). The vessel was placed on a Parr apparatus, evacuated and charged with hydrogen (~50 psi). The mixture was shaken at ambient temperature for 24 hours and then monitored for completion by HPLC/mass-spec. The reaction was re-charged with additional catalyst and hydrogen and maintained at ambient temperature for an additional 24 hours. The reaction mixture was filtered through a 0.2 micron PTFE membrane filter and the filtrate was concentrated to dryness under reduced pressure. Purification using a HORIZON HPFC system (silica cartridge, 0-10% CMA/chloroform) followed by recrystallization from acetonitrile provided 0.16 g of 3-[2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]-*N,N*-dimethylpropanamide as a white crystalline solid, 176-178 °C. MS (APCI) *m/z* 395 $(M + H)^+$; Anal. Calcd for $C_{23}H_{30}N_4O_2$: C, 70.02; H, 7.66; N, 14.20. Found: C, 69.83; H, 7.62; N, 14.26.

Example 354

3-[2-Ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]propanoic acid



Part A

A thick walled glass vessel, equipped with stir bar, was charged with a warmed solution of 7-bromo-2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (3.7 g, 10.0 mmol) in *N*,*N*-dimethylformamide (70 mL). To the solution was added in succession a solution of palladium acetate (224 mg, 1.0 mmol) and tri-ortho-tolylphosphine (608 mg, 2.0 mmol) in *N*,*N*-dimethylformamide (10 mL); triethylamine (4.2 mL, 30.0 mmol); and a solution of ethyl acrylate (1.2 g, 12.0 mmol) in *N*,*N*-dimethylformamide (2 mL). The reaction mixture was purged with nitrogen and the vessel was sealed and heated to 120 °C for 18 hours. The reaction vessel was cooled to ambient temperature. The reaction mixture was transferred to a round bottom flask and concentrated to dryness under reduced pressure. The resulting solid was dissolved in dichloromethane (150 mL) and washed with saturated potassium carbonate solution. The fractions were separated. The organic fraction was dried ($MgSO_4$) and concentrated. Purification using a HORIZON HPFC system (silica cartridge, 0-12% CMA/chloroform) followed by recrystallization from acetonitrile provided 2.5 g of ethyl (2*E*)-3-[2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]prop-2-enoate as a white solid, mp 210-212 °C. MS (APCI) *m/z* 394 $(M + H)^+$; Anal. Calcd for $C_{23}H_{27}N_3O_3$: C, 70.21; H, 6.92; N, 10.68. Found: C, 70.19; H, 6.93; N, 10.67.

Part B

A glass Parr bottle (500 mL) was charged with 10% palladium on carbon (0.25 g) wetted with ethanol (5 mL) and a slurry of ethyl (2*E*)-3-[2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]prop-2-enoate (2.4 g, 6.1 mmol) in methanol (250 mL). The vessel was placed on a Parr apparatus, evacuated and charged with hydrogen (~50 psi). The mixture was then shaken at ambient temperature for 48 hours. The reaction was monitored by HPLC/mass-spec and found to be complete. The reaction

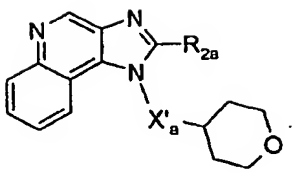
mixture was filtered through a 0.2 micron PTFE membrane filter and the filtrate was concentrated to dryness under reduced pressure. Purification using a HORIZON HPFC system (silica cartridge, 0-11% CMA/chloroform) followed by recrystallization from 60:30 hexane/ethyl acetate (30 mL) provided 1.9 g of ethyl 3-[2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]propanoate as a white crystalline solid, mp 113-115 °C. MS (APCI) *m/z* 396 $(M + H)^+$; Anal. Calcd for $C_{23}H_{29}N_3O_3 \cdot 0.75\ H_2O$: C, 67.54; H, 7.52; N, 10.27. Found: C, 67.25; H, 7.67; N, 10.26.

Part C

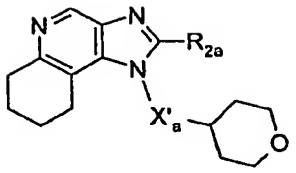
To a stirred solution of ethyl 3-[2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]propanoate (1.8 g, ) in methanol (3 mL) was added Claisen's alkali (5 mL). The reaction mixture was heated to 70 °C and maintained for 18 hours. The reaction mixture was removed from the heat and treated with citric acid, adjusting to pH=5. The mixture was then concentrated to dryness under reduced pressure. The resulting solid was taken up in water and neutralized to pH=7 with saturated potassium carbonate solution. A white crystalline solid formed. The crystalline solid was collected by vacuum filtration and air dried to provide 1.4 g of 3-[2-ethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-7-yl]propanoic acid as a white solid, mp 198-200 °C. MS (APCI) *m/z* 368 $(M + H)^+$; Anal. Calcd for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.42; H, 6.67; N, 11.35.

Exemplary Compounds and Pharmaceutical Compositions

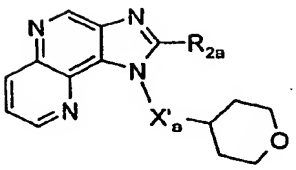
Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (IIb, IIIa, IVb, Vb, or VIa) and an $X'_a$ group and an $R_{2a}$ substituent shown in the following table, wherein each line of the table is matched with the Formula (IIb, IIIa, IVb, Vb, or VIa) to represent a specific embodiment of a compound (or pharmaceutically acceptable salt thereof) of the invention or a pharmaceutical composition of the invention comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of the specific embodiment of a compound (or a pharmaceutically acceptable salt thereof).



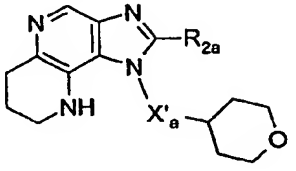
IIb



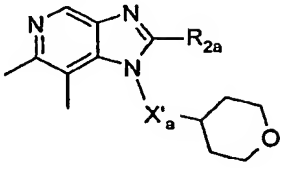
IIIa



IVb



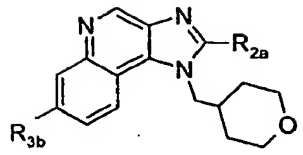
VIa



Vb

| $X'_a$ | $R_{2a}$ |
|---|---|
| -NH- | *n*-propyl |
| -NH- | *n*-butyl |
| -NH- | methoxymethyl |
| -NH- | ethoxymethyl |
| -NH- | 2-methoxyethyl |
| $-CH_2-$ | *n*-propyl |
| $-CH_2-$ | *n*-butyl |
| $-CH_2-$ | methoxymethyl |
| $-CH_2-$ | ethoxymethyl |
| $-CH_2-$ | 2-methoxyethyl |

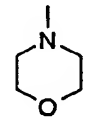
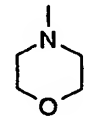
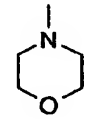
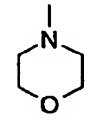
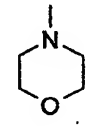
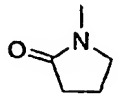
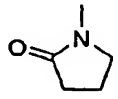
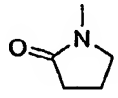
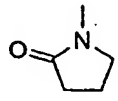
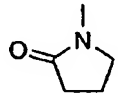
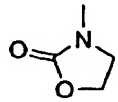
Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (IIc) and an $R_{2a}$ and an $R_{3b}$ substituent shown in the following table, wherein each line of the table is matched with the Formula (IIc) to represent a specific embodiment of a compound, a therapeutically effective amount of which (or a pharmaceutically acceptable salt thereof) in combination with a pharmaceutically acceptable carrier is a specfic embodiment of a pharmaceutical composition of the invention.

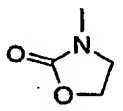
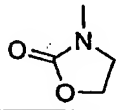
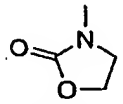
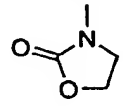


IIc

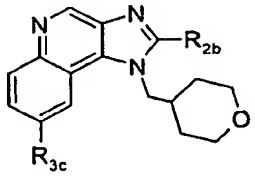
| $R_{2a}$ | $R_{3b}$ |
|---|---|
| *n*-propyl | 4-(aminomethyl)phenyl |
| *n*-butyl | 4-(aminomethyl)phenyl |
| methoxymethyl | 4-(aminomethyl)phenyl |
| ethoxymethyl | 4-(aminomethyl)phenyl |
| 2-methoxyethyl | 4-(aminomethyl)phenyl |
| *n*-propyl | 3-(methylsulfonylamino)phenyl |
| *n*-butyl | 3-(methylsulfonylamino)phenyl |
| methoxymethyl | 3-(methylsulfonylamino)phenyl |
| ethoxymethyl | 3-(methylsulfonylamino)phenyl |
| 2-methoxyethyl | 3-(methylsulfonylamino)phenyl |
| *n*-propyl | 2-hydroxyphenyl |
| *n*-butyl | 2-hydroxyphenyl |
| methoxymethyl | 2-hydroxyphenyl |
| ethoxymethyl | 2-hydroxyphenyl |
| 2-methoxyethyl | 2-hydroxyphenyl |
| *n*-propyl | 3-hydroxyphenyl |
| *n*-butyl | 3-hydroxyphenyl |
| methoxymethyl | 3-hydroxyphenyl |
| ethoxymethyl | 3-hydroxyphenyl |
| 2-methoxyethyl | 3-hydroxyphenyl |
| *n*-propyl | 4-hydroxyphenyl |
| *n*-butyl | 4-hydroxyphenyl |
| methoxymethyl | 4-hydroxyphenyl |
| ethoxymethyl | 4-hydroxyphenyl |

| | |
|---|---|
| 2-methoxyethyl | 4-hydroxyphenyl |
| *n*-propyl | 2-(hydroxymethyl)phenyl |
| *n*-butyl | 2-(hydroxymethyl)phenyl |
| methoxymethyl | 2-(hydroxymethyl)phenyl |
| ethoxymethyl | 2-(hydroxymethyl)phenyl |
| 2-methoxyethyl | 2-(hydroxymethyl)phenyl |
| *n*-propyl | 3-(hydroxymethyl)phenyl |
| *n*-butyl | 3-(hydroxymethyl)phenyl |
| methoxymethyl | 3-(hydroxymethyl)phenyl |
| ethoxymethyl | 3-(hydroxymethyl)phenyl |
| 2-methoxyethyl | 3-(hydroxymethyl)phenyl |
| *n*-propyl | 4-(hydroxymethyl)phenyl |
| *n*-butyl | 4-(hydroxymethyl)phenyl |
| methoxymethyl | 4-(hydroxymethyl)phenyl |
| ethoxymethyl | 4-(hydroxymethyl)phenyl |
| 2-methoxyethyl | 4-(hydroxymethyl)phenyl |
| *n*-propyl | pyridin-3-yl |
| *n*-butyl | pyridin-3-yl |
| methoxymethyl | pyridin-3-yl |
| ethoxymethyl | pyridin-3-yl |
| 2-methoxyethyl | pyridin-3-yl |
| *n*-propyl | pyridin-4-yl |
| *n*-butyl | pyridin-4-yl |
| methoxymethyl | pyridin-4-yl |
| ethoxymethyl | pyridin-4-yl |
| 2-methoxyethyl | pyridin-4-yl |
| *n*-propyl | (cyclopropylmethyl)amino |
| *n*-butyl | (cyclopropylmethyl)amino |
| methoxymethyl | (cyclopropylmethyl)amino |
| ethoxymethyl | (cyclopropylmethyl)amino |
| 2-methoxyethyl | (cyclopropylmethyl)amino |

| | |
|---|---|
| *n*-propyl |  |
| *n*-butyl |  |
| methoxymethyl |  |
| ethoxymethyl |  |
| 2-methoxyethyl |  |
| *n*-propyl |  |
| *n*-butyl |  |
| methoxymethyl |  |
| ethoxymethyl |  |
| 2-methoxyethyl |  |
| *n*-propyl |  |

| | |
|---|---|
| *n*-butyl |  |
| methoxymethyl |  |
| ethoxymethyl |  |
| 2-methoxyethyl |  |

Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (IId) and an $R_{2b}$ and an $R_{3c}$ substituent shown in the following table, wherein each line of the table is matched with the Formula (IId) to represent a specific embodiment of a compound, a therapeutically effective amount of which (or a pharmaceutically acceptable salt thereof) in combination with a pharmaceutically acceptable carrier is a specfic embodiment of a pharmaceutical composition of the invention.



IId

| $R_{2b}$ | $R_{3c}$ |
|---|---|
| *n*-butyl | 4-(aminomethyl)phenyl |
| 2-methoxyethyl | 4-(aminomethyl)phenyl |
| *n*-butyl | 3-(methylsulfonylamino)phenyl |
| 2-methoxyethyl | 3-(methylsulfonylamino)phenyl |
| *n*-butyl | 2-hydroxyphenyl |
| 2-methoxyethyl | 2-hydroxyphenyl |

| | |
|---|---|
| *n*-butyl | 3-hydroxyphenyl |
| 2-methoxyethyl | 3-hydroxyphenyl |
| *n*-butyl | 4-hydroxyphenyl |
| 2-methoxyethyl | 4-hydroxyphenyl |
| *n*-butyl | 2-(hydroxymethyl)phenyl |
| 2-methoxyethyl | 2-(hydroxymethyl)phenyl |
| *n*-butyl | 3-(hydroxymethyl)phenyl |
| 2-methoxyethyl | 3-(hydroxymethyl)phenyl |
| *n*-butyl | 4-(hydroxymethyl)phenyl |
| 2-methoxyethyl | 4-(hydroxymethyl)phenyl |
| *n*-butyl | pyridin-3-yl |
| 2-methoxyethyl | pyridin-3-yl |
| *n*-butyl | pyridin-4-yl |
| 2-methoxyethyl | pyridin-4-yl |

Compounds described herein have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α in human cells when tested using one of the methods described below.

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham

Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x $10^6$ cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014 μM). The final concentration of PBMC suspension is 2 x $10^6$ cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN-α by ELISA and for TNF-α by IGEN/BioVeris Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN-α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF-α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF-α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α and IFN-α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested

cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

CYTOKINE INDUCTION IN HUMAN CELLS

(High Throughput Screen)

The CYTOKINE INDUCTION IN HUMAN CELLS test method described above was modified as follows for high throughput screening.

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at $4 \times 10^6$ cells/mL in RPMI complete (2-fold the final cell density). The PBMC suspension is added to 96-well flat bottom sterile tissue culture plates.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The compounds are generally tested at concentrations ranging from 30 - 0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with a reference compound 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) on each plate. The solution of test compound is added at 7.5 mM to the first well of a dosing plate and serial 3 fold dilutions are made for the 7 subsequent concentrations in DMSO. RPMI Complete media is then added to the test compound dilutions in order to reach a final compound concentration of 2-fold higher (60 - 0.028 μM) than the final tested concentration range.

Incubation

Compound solution is then added to the wells containing the PBMC suspension bringing the test compound concentrations to the desired range (usually 30 - 0.014 μM) and the DMSO concentration to 0.4 %. The final concentration of PBMC suspension is $2x10^6$ cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 g) at 4°C. 4-plex Human Panel MSD MULTI-SPOT 96-well plates are pre-coated with the appropriate capture antibodies by MesoScale Discovery, Inc. (MSD, Gaithersburg, MD). The cell-free culture supernatants are removed and transferred to the MSD plates. Fresh samples are typically tested, although they may be maintained at -30 to -70°C until analysis.

Interferon-α and Tumor Necrosis Factor-α Analysis

MSD MULTI-SPOT plates contain within each well capture antibodies for human TNF-α and human IFN-α that have been pre-coated on specific spots. Each well contains four spots: one human TNF-α capture antibody (MSD) spot, one human IFN- α capture antibody (PBL Biomedical Laboratories, Piscataway, NJ) spot, and two inactive bovine serum albumin spots. The human TNF-α capture and detection antibody pair is from MesoScale Discovery. The human IFN-α multi-subtype antibody (PBL Biomedical Laboratories) captures all IFN-α subtypes except IFN-α F (IFNA21). Standards consist of recombinant human TNF-α (R&D Systems, Minneapolis, MN) and IFN-α (PBL Biomedical Laboratories). Samples and separate standards are added at the time of analysis to each MSD plate. Two human IFN-α detection antibodies (Cat. Nos. 21112 & 21100, PBL) are used in a two to one ratio (weight:weight) to each other to determine the IFN-α concentrations. The cytokine-specific detection antibodies are labeled with the SULFO-TAG reagent (MSD). After adding the SULFO-TAG labeled detection antibodies to the wells, each well's electrochemoluminescent levels are read using MSD's SECTOR HTS READER. Results are expressed in pg/mL upon calculation with known cytokine standards.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α or IFN-α (y-axis) as a function of compound concentration (x-axis).

A plate-wise scaling is performed within a given experiment aimed at reducing plate-to-plate variability associated within the same experiment. First, the greater of the median DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. Negative values that may result from background subtraction are set to zero. Each plate within a given experiment has a reference compound that serves as a control. This control is used to calculate a median expected area under the curve across all plates in the assay. A plate-wise scaling factor is calculated for each plate as a ratio of the area of the reference compound on the particular plate to the median expected area for the entire experiment. The data from each plate are then multiplied by the plate-wise scaling factor for all plates. Only data from plates bearing a scaling factor of between 0.5 and 2.0 (for both cytokines IFN-α; TNF-α) are reported. Data from plates with scaling factors outside the above mentioned interval are retested until they bear scaling factors inside the above mentioned interval. The above method produces a scaling of the y-values without altering the shape of the curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91). The median expected area is the median area across all plates that are part of a given experiment.

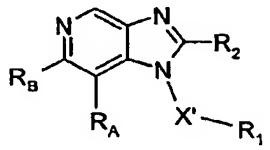
A second scaling may also be performed to reduce inter-experiment variability (across multiple experiments). All background-subtracted values are multiplied by a single adjustment ratio to decrease experiment-to-experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on an average of previous experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from an average of previous experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula I:



I

wherein:

X' is selected from the group consisting of -$CH_2$-, -NH-, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of -$NH_2$, -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl, -$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

$R_A$ and $R_B$ taken together form a fused benzene or pyridine ring which is unsubstituted or substituted by one or two R groups, or substituted by one $R_3$ group, or substituted by one $R_3$ group and one R group; wherein the fused pyridine ring is

wherein the highlighted bond indicates the position where the ring is fused; and wherein $R_3$ is at the 7- or 8-position;

or $R_A$ and $R_B$ taken together form a fused cyclohexene or tetrahydropyridine ring which is unsubstituted or substituted at a carbon atom by one or more R groups; wherein the fused tetrahydropyridine ring is

wherein the highlighted bond indicates the position where the ring is fused;

or $R_A$ is alkyl, and $R_B$ is hydrogen or alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

$R_3$ is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$,

$-Z-X-R_5$, and

$-NH-Q-R_4$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

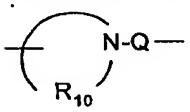
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

$-O-N=C(R_4)-$,

-C(=N-O-$R_8$)-,

-CH(-N(-O-$R_8$)-Q-$R_4$)-,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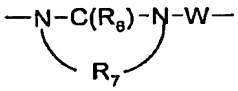
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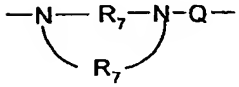
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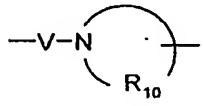
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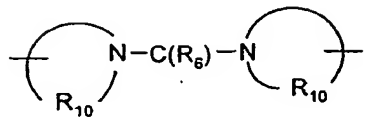
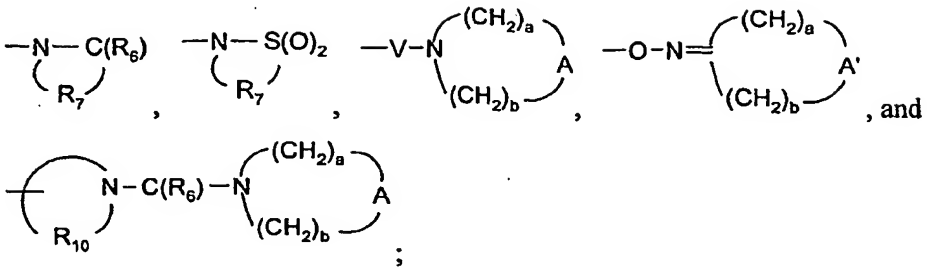

;

Z is a bond or -O-;

$R_4$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

$R_5$ is selected from the group consisting of:



;

$R_6$ is selected from the group consisting of =O and =S;

$R_7$ is $C_{2-7}$ alkylene;

$R_8$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, hydroxy-$C_{1-10}$ alkylenyl, $C_{1-10}$ alkoxy-$C_{1-10}$ alkylenyl, aryl-$C_{1-10}$ alkylenyl, and heteroaryl-$C_{1-10}$ alkylenyl;

$R_9$ is selected from the group consisting of hydrogen and alkyl;

$R_{10}$ is $C_{3-8}$ alkylene;

A is selected from the group consisting of -$CH_2$-, -O-, -C(O)-, -$S(O)_{0-2}$-, and –N(-Q-$R_4$)-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-$R_4$)-, and -$CH_2$-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, -$C(R_6)$-S-, and -$C(R_6)$-$N(OR_9)$-;

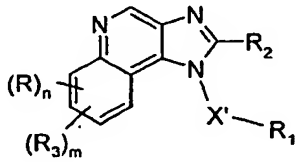
V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq 7$;

or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula II:



II

wherein:

X' is selected from the group consisting of -$CH_2$-, -NH-, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of -$NH_2$, -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl, -$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

-$N(R_9)_2$;

n is 0, 1, or 2;

$R_3$ is selected from the group consisting of:

-Z-$R_4$,

-Z-X-$R_4$,

-Z-X-Y-$R_4$,

-Z-X-Y-X-Y-$R_4$,

-Z-X-$R_5$, and

-NH-Q-$R_4$;

$R_3$ is at the 7- or 8-position;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-S(O)$_{0-2}$-,

-S(O)$_2$-N($R_8$)-,

-C($R_6$)-,

-C($R_6$)-O-,

-O-C($R_6$)-,

-O-C(O)-O-,

-N($R_8$)-Q-,

-C($R_6$)-N($R_8$)-,

-O-C($R_6$)-N($R_8$)-,

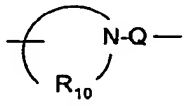
-C($R_6$)-N(O$R_9$)-,

-O-N($R_8$)-Q-,

-O-N=C($R_4$)-,

-C(=N-O-$R_8$)-,

-CH(-N(-O-$R_8$)-Q-$R_4$)-,



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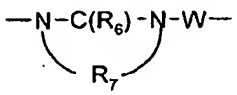

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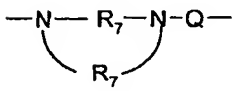

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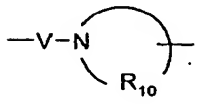

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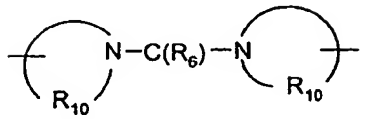


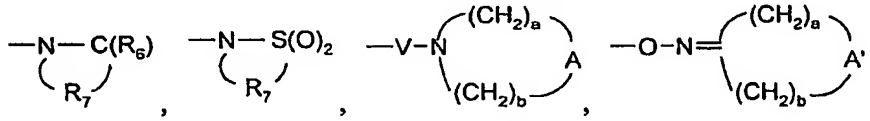
;

Z is a bond or -O-;

$R_4$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,

alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

$R_5$ is selected from the group consisting of:




;

$R_6$ is selected from the group consisting of =O and =S;

$R_7$ is $C_{2-7}$ alkylene;

$R_8$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, hydroxy-$C_{1-10}$ alkylenyl, $C_{1-10}$ alkoxy-$C_{1-10}$ alkylenyl, aryl-$C_{1-10}$ alkylenyl, and heteroaryl-$C_{1-10}$ alkylenyl;

$R_9$ is selected from the group consisting of hydrogen and alkyl;

$R_{10}$ is $C_{3-8}$ alkylene;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(-Q-R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

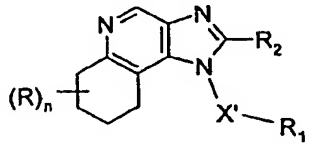
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq 7$;

or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula III:



III

wherein:

X' is selected from the group consisting of -$CH_2$-, -NH-, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of -$NH_2$, -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl, -$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

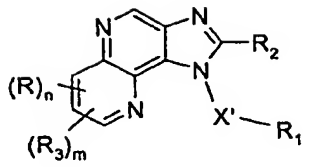
-$N(R_9)_2$;

n is 0, 1, or 2; and

$R_9$ is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula IV:



IV

wherein:

X' is selected from the group consisting of -$CH_2$-, -NH-, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of -$NH_2$, -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl, -$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

-$N(R_9)_2$;

n is 0, 1, or 2;

$R_3$ is selected from the group consisting of:

-Z-$R_4$,

-Z-X-$R_4$,

-Z-X-Y-$R_4$,

-Z-X-Y-X-Y-$R_4$,

-Z-X-$R_5$, and

-NH-Q-$R_4$;

$R_3$ is at the 7- or 8-position;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

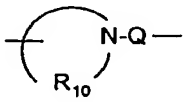
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

$-O-N=C(R_4)-$,

$-C(=N-O-R_8)-$,

$-CH(-N(-O-R_8)-Q-R_4)-$,



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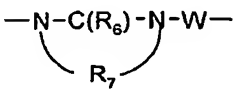

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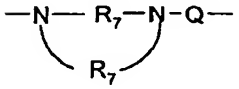

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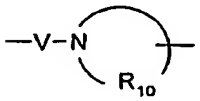

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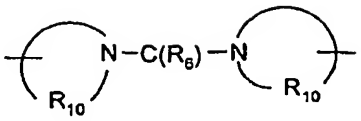
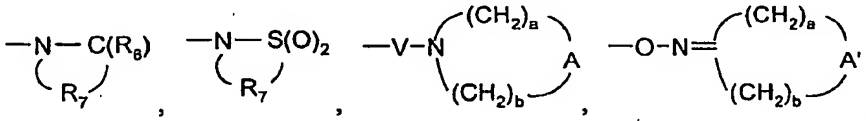


;

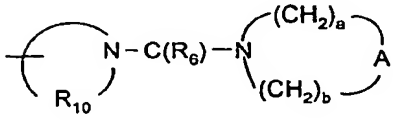
Z is a bond or -O-;

$R_4$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

$R_5$ is selected from the group consisting of:



, and



;

$R_6$ is selected from the group consisting of =O and =S;

$R_7$ is $C_{2-7}$ alkylene;

$R_8$ is selected from the group consisting of hydrogen, $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, hydroxy-$C_{1-10}$ alkylenyl, $C_{1-10}$ alkoxy-$C_{1-10}$ alkylenyl, aryl-$C_{1-10}$ alkylenyl, and heteroaryl-$C_{1-10}$ alkylenyl;

$R_9$ is selected from the group consisting of hydrogen and alkyl;

$R_{10}$ is $C_{3-8}$ alkylene;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(-Q-R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, -C($R_6$)-, -C($R_6$)-C($R_6$)-, -S(O)$_2$-, -C($R_6$)-N($R_8$)-W-, -S(O)$_2$-N($R_8$)-, -C($R_6$)-O-, -C($R_6$)-S-, and -C($R_6$)-N(O$R_9$)-;

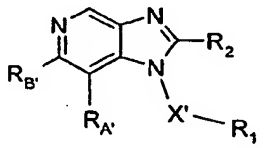
V is selected from the group consisting of -C($R_6$)-, -O-C($R_6$)-, -N($R_8$)-C($R_6$)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq 7$;

or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier in combination with a therapeutically effective amount of a compound of Formula V:



V

wherein:

X' is selected from the group consisting of -CH$_2$-, -NH-, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of -NH$_2$, -CH$_3$, -CH$_2$-C$_{1-4}$ alkyl, -CH$_2$-C$_{1-2}$ alkylenyl-O-C$_{1-2}$ alkyl, -CH$_2$-O-C$_{1-3}$ alkyl, -CH$_2$-OH, -CH$_2$-C$_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, C$_{1-4}$ alkyl, C$_{1-4}$ alkoxy, hydroxy, haloC$_{1-4}$ alkyl, and hydroxyC$_{1-4}$ alkyl;

$R_{A'}$ is alkyl, and $R_{B'}$ is hydrogen or alkyl;

or a pharmaceutically acceptable salt thereof.

6. The pharmaceutical composition of claim 5 wherein $R_{A'}$ and $R_{B'}$ are both methyl.

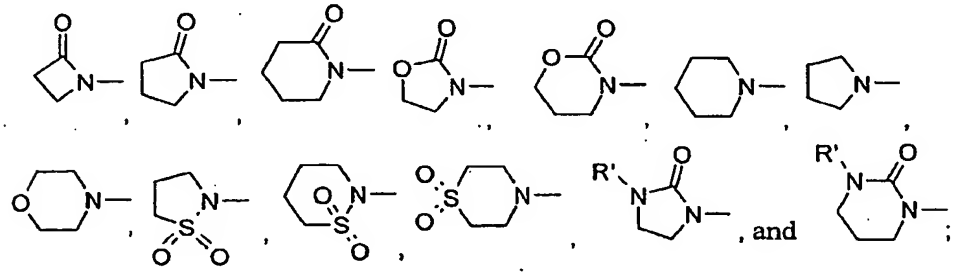
7. The pharmaceutical composition of any one of claims 1, 2, and 4 wherein $R_3$ is

-Z-$R_4$.

8. The pharmaceutical composition of claim 7 wherein $R_4$ is selected from the group consisting of aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl wherein the aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, aminoalkyl, halogen, hydroxy, cyano, amino, alkylamino, and dialkylamino; and Z is a bond.

9. The pharmaceutical composition of claim 7 wherein $R_4$ is a 4 to 7 membered heterocyclyl group which contains one or more ring nitrogen atoms and optionally a ring oxygen or ring sulfur atom, wherein the point of attachment of the heterocyclyl group is one of the nitrogen atoms, and wherein the heterocyclyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of oxo, alkyl, and arylalkylenyl; and Z is a bond.

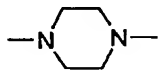
10. The pharmaceutical composition of claim 9 wherein the heterocyclyl group is selected from the group consisting of:




wherein R' is alkyl.

11. The pharmaceutical composition of any one of claims 1, 2, and 4 wherein $R_3$ is -Z-X-Y-$R_4$.

12. The pharmaceutical composition of claim 11 wherein $R_4$ is selected from the group consisting of hydrogen, alkyl, and heterocyclyl; Y is selected from the group consisting of -$S(O)_2$-, -C(O)-, -C(O)-NH-, and -NH-$S(O)_2$-; X is phenylene; and Z is a bond.

13. The pharmaceutical composition of claim 11 wherein $R_4$ is selected from the group consisting of alkyl, aryl, arylalkylenyl, and heteroaryl, each of which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, and alkyl; Y is selected from the group consisting of $-S(O)_2-$, -C(O)-, and -C(O)-N($R_8$)-; X is  ; and Z is a bond.

14. The pharmaceutical composition of claim 11 wherein $R_4$ is hydrogen or alkyl; Y is -C(O)-N($R_8$)- or -C(O)-O-; $R_8$ is $C_{1-4}$ alkyl; X is alkylene or alkenylene; and Z is a bond.

15. The pharmaceutical composition of claim 11 wherein $R_4$ is alkyl substituted by maleimidyl; Y is -NHC(O)-; X is alkylene interrupted by one -O- group; and Z is -O-.

16. The pharmaceutical composition of any one of claims 1, 2, and 4 wherein $R_3$ is $-Z-X_f-Y_a-X_g-Y_b-R_4$, and wherein $R_4$ is hydrogen or $C_{1-4}$ alkyl, $Y_b$ is -C(O)-O-, $X_g$ is alkylene, $Y_a$ is -NHC(O)-, $X_f$ is alkylene interrupted by one -O- group, and Z is -O-.

17. The pharmaceutical composition of any one of claims 1, 2, 4, 7, and 8 wherein $R_3$ is selected from the group consisting of hydroxyphenyl, (hydroxymethyl)phenyl, (aminomethyl)phenyl, pyridin-3-yl, and pyridin-4-yl.

18. The pharmaceutical composition of any one of claims 1, 2, 4, 11, and 12 wherein $R_3$ is (methylsulfonylamino)phenyl.

19. The pharmaceutical composition of claim 1 or 2 wherein $R_3$ is selected from the group consisting of hydroxyphenyl, (hydroxymethyl)phenyl, 4-(aminomethyl)phenyl, 3-(methylsulfonylamino)phenyl, pyridin-3-yl, and pyridin-4-yl.

20. The pharmaceutical composition of claim 1 or 4 wherein $R_3$ is selected from the group consisting of hydroxyphenyl, (hydroxymethyl)phenyl, and (methylsulfonylamino)phenyl.

21. The pharmaceutical composition of any one of claims 1, 2, 4, and 7 through 20 wherein $R_3$ is at the 7-position.

22. The pharmaceutical composition of any one of claims 1, 2, 4, and 7 through 20 wherein $R_3$ is at the 8-position.

23. The pharmaceutical composition of any one of claims 2, 3, 4, and 7 through 22 except as dependent on claim 1 wherein n is 0.

24. The pharmaceutical composition of claim 2 or 4 wherein m is 0.

25. The pharmaceutical composition of claim 2 or 4 wherein m and n are both 0.

26. The pharmaceutical composition of any one of claims 1 through 25 wherein $R_2$ is selected from the group consisting of $-CH_3$, $-CH_2-C_{1-4}$ alkyl, $-CH_2-O-C_{1-3}$ alkyl, $-CH_2-C_{1-2}$ alkylenyl-$O-C_{1-2}$ alkyl, $-CH_2-OH$, and $-CH_2-C_{1-3}$ alkylenyl-OH.

27. The pharmaceutical composition of claim 26 wherein $R_2$ is selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, cyclopropylmethyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

28. The pharmaceutical composition of claim 27 wherein $R_2$ is selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, cyclopropylmethyl, methoxymethyl, ethoxymethyl, and 2-methoxyethyl.

29. The pharmaceutical composition of claim 28 wherein $R_2$ is selected from the group consisting of *n*-propyl, *n*-butyl, methoxymethyl, ethoxymethyl, and 2-methoxyethyl.

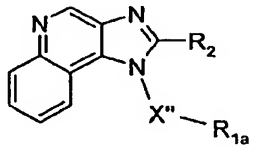
30. The pharmaceutical composition of any one of claims 1 through 29 wherein $R_1$ is tetrahydo-2*H*-pyran-4-yl.

31. The pharmaceutical composition of any one of claims 1 through 30 wherein X' is $-CH_2-$.

32. The pharmaceutical composition of any one of claims 1 through 30 wherein X' is -NH-.

33. The pharmaceutical composition of any one of claims 1 through 30 wherein X' is -O-.

34. A compound of Formula IIa:



IIa

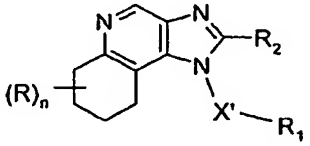
wherein:

X" is $-CH_2-$;

$R_{1a}$ is selected from the group consisting of tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl; and

$R_2$ is selected from the group consisting of $-CH_3$, $-CH_2-C_{1-4}$ alkyl, $-CH_2-C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, $-CH_2-O-C_{1-3}$ alkyl, $-CH_2-OH$, $-CH_2-C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;
or a pharmaceutically acceptable salt thereof.

35. A compound of Formula III:



III

wherein:

X' is selected from the group consisting of -$CH_2$-, -NH-, and -O-;

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of -$NH_2$, -$CH_3$, -$CH_2$-$C_{1-4}$ alkyl, -$CH_2$-$C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, -$CH_2$-O-$C_{1-3}$ alkyl, -$CH_2$-OH, -$CH_2$-$C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

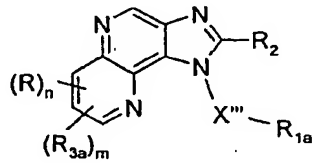
-$N(R_9)_2$;

n is 0, 1, or 2; and

$R_9$ is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

36. A compound of Formula IVa:



IVa

wherein:

X''' is -$CH_2$-

$R_{1a}$ is selected from the group consisting of tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of $-NH_2$, $-CH_3$, $-CH_2-C_{1-4}$ alkyl, $-CH_2-C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, $-CH_2-O-C_{1-3}$ alkyl, $-CH_2-OH$, $-CH_2-C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

n is 0, 1, or 2;

$R_{3a}$ is selected from the group consisting of:

$-Z-R_4$ and

$-Z-X-R_4$;

$R_{3a}$ is at the 7- or 8-position.

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Z is a bond or -O-;

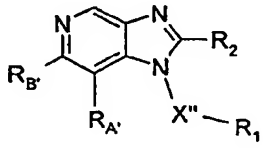
$R_4$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected

from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and

$R_9$ is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

37. A compound of Formula Va:



Va

wherein:

X" is $-CH_2-$

$R_1$ is selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydo-2*H*-pyran-2-yl, tetrahydo-2*H*-pyran-3-yl, tetrahydo-2*H*-pyran-4-yl, tetrahydo-2*H*-thiopyran-4-yl, and 1,1-dioxidotetrahydo-2*H*-thiopyran-4-yl;

$R_2$ is selected from the group consisting of $-NH_2$, $-CH_3$, $-CH_2-C_{1-4}$ alkyl, $-CH_2-C_{1-2}$ alkylenyl-O-$C_{1-2}$ alkyl, $-CH_2-O-C_{1-3}$ alkyl, $-CH_2-OH$, $-CH_2-C_{1-3}$ alkylenyl-OH, and benzyl wherein the phenyl ring of the benzyl group is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, hydroxy, halo$C_{1-4}$ alkyl, and hydroxy$C_{1-4}$ alkyl;

$R_{A'}$ is alkyl, and $R_{B'}$ is hydrogen or alkyl;

or a pharmaceutically acceptable salt thereof.

38. The compound or salt of claim 37 wherein $R_{A'}$ and $R_{B'}$ are both methyl.

39. The compound or salt of claim 35 wherein X' is $-CH_2-$.

40. The compound or salt of claim 35 wherein X' is -NH-.

41. The compound or salt of claim 35 wherein X' is -O-.

42. The compound or salt of claim 36 wherein $R_{3a}$ is selected from the group consisting of hydroxyphenyl and (hydroxymethyl)phenyl.

43. The compound or salt of any one of claims 35, 36, and 39 through 42 wherein n is 0.

44. The compound or salt of claim 36 wherein m is 0.

45. The compound or salt of claim 36 wherein m and n are both 0.

46. The compound or salt of any one of claims 34, 36, 42, 43 as dependent on claim 36 or 42, 44, and 45 wherein $R_{1a}$ is tetrahydo-2*H*-pyran-4-yl.

47. The compound or salt of any one of claims 35, 37, 38, 39, 40, 41, and 43 as dependent on claim 35, 39, 40, or 41 wherein $R_1$ is tetrahydo-2*H*-pyran-4-yl.

48. The compound or salt of any one of claims 34 through 47 wherein $R_2$ is selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, cyclopropylmethyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, hydroxymethyl, and 2-hydroxyethyl.

49. The compound or salt of claim 48 wherein $R_2$ is selected from the group consisting of *n*-propyl, *n*-butyl, methoxymethyl, ethoxymethyl, and 2-methoxyethyl.

50. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 34 through 49 in combination with a pharmaceutically acceptable carrier.

51. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a pharmaceutical composition of any one of claims 1 through 33 and 50 or a compound or salt of any one of claims 34 through 49 to the animal.

52. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a pharmaceutical composition of any one of claims 1 through 33 and 50 or a compound or salt of any one of claims 34 through 49 to the animal.

53. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a pharmaceutical composition of any one of claims 1 through 33 and 50 or a compound or salt of any one of claims 34 through 49 to the animal.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/048017

## A. CLASSIFICATION OF SUBJECT MATTER

*A61K 31/437(2006.01)i, A61P 37/02(2006.01)i*

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC8 A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN(Registry, Caplus), eKIPASS (imidazoquinoline, imidazonaphthyridine, imidazopyridine, cytokine biosynthesis, viral, neoplastic)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2004/058759 A1 (3M INNOVATIVE PROPERTIES COMPANY) 15 July 2004<br>See the compound of formula (XLVII) on page 444. | 1, 2, 7 - 16, 19, 20, 24, 25, 34 |
| A | WO 2005/076783 A2 (3M INNOVATIVE PROPERTIES COMPANY) 25 August 2005<br>See the compound of formula XXIIIa on page 199. | 1 - 16, 19, 20, 24, 25, 34 - 45 |
| A | WO 2005/066169 A2 (3M INNOVATIVE PROPERTIES COMPANY) 21 July 2005<br>See the compounds of formulae (XII), (XIII), (XIV), and (XV) on pages 207, 210, 213, and 216. | 1 - 16, 19, 20, 24, 25, 34 - 45 |
| A | WO 2005/018551 A2 (3M INNOVATIVE PROPERTIES COMPANY) 03 March 2005<br>See the compound of formula (I) on page 252. | 1 - 16, 19, 20, 24, 25, 34 - 45 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 17 APRIL 2007 (17.04.2007) | **17 APRIL 2007 (17.04.2007)** |

| Name and mailing address of the ISA/KR | Authorized officer |
|---|---|
| Korean Intellectual Property Office<br>920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea<br>Facsimile No. 82-42-472-7140 | LEE, Mi Jeong<br>Telephone No. 82-42-481-5601 |

Form PCT/ISA/210 (second sheet) (April 2007)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/048017

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 51-53
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 51-53 pertain to methods for treatment of the human or animal body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☒ Claims Nos.: 27-29, 49
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 27-29,49 are singularly dependent claims. But each of claims 27, 49 depends from a multiple dependent claim directly, and each of claims 28, 29 depends from a multiple dependent claim indirectly. Thus, claims 27-29,49 are unsearchable because they are referring to multiple dependent claims which are not drafted in accordance with the third sentence of Rule 6.4 (a).

3. ☒ Claims Nos.: 17, 18, 21-23, 26, 30-33, 46-48, 50-53
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Group I : RA and RB of the active compound form a fused benzene ring in claim 1(in part), claims 7-16 (in part), claims 2, 19, 20, 24, 25, and 34.

Group II: RA and RB of the active compound form a fused tetrahydropyridine ring in claim 1(in part), claim 43(in part), claims 36, 42, 44, and 45.

Group III: RA and RB of the active compound form a fused cyclohexene ring in claim 1(in part), claim 43(in part), claim 3, claim 35, and claims 39-41.

Group IV: RA and RB of the active compound form a fused pyridine ring in claim 1(in part), claims 7-16(in part), claims 4, 20, 24, and 25.

Group V: RA' is alkyl, and RB' is hydrogen or alkyl in claims 5, 6, 37, 38.

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2006/048017

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | CN 1914203 A | 14.02.2007 |
| | | CA 2549216 AA | 25.08.2005 |
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